

Respiratory Decompensation in Preterm Infants Following Surgical Ligation or Device Closure
of the Patent Ductus Arteriosus

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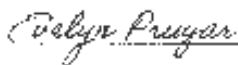
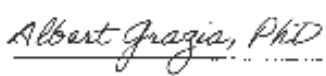
Decompensation in Preterm Infants Following Surgical Ligation or Device Closure
of the Patent Ductus Arteriosus

Craig R. Wheeler

Approval of the Dissertation

This Dissertation, by Craig Wheeler has been approved by the committee members below, who recommend it be accepted by the University of Bridgeport, College of Health Sciences in partial fulfillment of requirements for the degree of Doctor of Health Sciences (D.H.Sc.)

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Abstract

Background: Temporal derangements in oxygenation and ventilation have been associated with surgical ligation and device closure of the ductus arteriosus. We sought to evaluate respiratory decompensation, defined as an increase of Respiratory Severity Score (RSS) >50% above pre-procedural value following surgical ligation (SL) or transcatheter PDA closure (TCPC). *Methods:* Premature infants <37 weeks gestational age who underwent invasive mechanical ventilation before and after PDA closure were included in the study. Included infants were grouped according to procedure type (SL or TCPC) and need for rescue high-frequency ventilation (HFV). RSS > 50% above baseline and HFV usage were measured at six intervals, from admission through 24-hours post-procedure. The Mann-Whitney *U*-test was used to assess differences in continuous variables and the chi-square and Fisher exact tests were utilized for categorical variables. The Holm-Sidak procedure was used to correct for multiple comparisons. *Results:* 110 infants, (n = 88) SL and (n = 22) TCPC were included for analysis. Twelve-hours post-procedure RSS > 50% was observed in 40% of SL compared to 3% of TCPC ($p = .021$) and rescue HFV at 24-hours was (42% vs. 5%, $p = .004$) for SL and TCPC respectively. Rescue HFV was associated with SL (92% vs. 8%, $p = .008$), smaller gestational age (25 vs. 26 weeks, $p = .003$) and younger age at PDA closure (19 vs. 25 days, $p = .003$). *Conclusion:* In this study, we found that respiratory decompensation following closure of the PDA was associated with younger gestational age, younger age at PDA closure, surgical ligation, and elevated RSS values over the first 12 hours after closure. These results confirm prior data, but also suggest that an elevated RSS following PDA closure may be a useful non-invasive bedside tool to identify the respiratory phenotype of post ligation cardiac syndrome.

Keywords: patent ductus arteriosus, prematurity, respiratory severity score, high-frequency ventilation

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Introduction

The ductus arteriosus (DA) is a critical component of fetal circulation anatomically located between the pulmonary artery and aorta. In utero, the fetus receives oxygenated blood from the placenta, and blood is shunted away from the high resistance of the pulmonary vascular bed into the systemic circulation (Homma et al., 2016). Following birth, the placental circulation is removed, pulmonary vascular resistance falls, and the pulmonary circulation becomes the source of oxygenated blood; hence, left-to-right shunting through the ductus is no longer required and can have a deleterious impact on the infant (Rios et al., 2018). Spontaneous closure of the DA occurs within 12 to 40-hours in the majority (>95%) of infants born >28 weeks of gestation (Jain et al., 2014; Rios et al., 2018). In contrast, persistent patent ductus arteriosus (PDA) is defined as a failure of the ductus to close within 72-hours postnatal age. Persistent PDA is observed in 70% of infants born <28 weeks and 80% for those born at 24-25 weeks gestation (Heuchan & Clyman, 2014; Rolland et al., 2015).

PDA is the most commonly observed cardiovascular abnormality during the first year of life in preterm infants (Weisz & McNamara, 2014). A persistent PDA shunts blood away from the descending aorta and into the pulmonary artery, which may result in hemodynamic and cardiovascular abnormalities. These abnormalities include increased pulmonary blood flow resulting in pulmonary over circulation with concurrent hypoperfusion of the gastrointestinal and cerebral circulations (Noori et al., 2009; Vali et al., 2019). Although no universal definition exists; PDA is considered hemodynamically significant (HsPDA) based upon the size, magnitude of shunt volume, and echocardiographic markers of systemic hypoperfusion and pulmonary over circulation (Lee, 2019). Further, HsPDA may result in heart failure, end-organ dysfunction, prolonged mechanical ventilation, supplemental oxygen dependency, bronchopulmonary

dysplasia (BPD), neurologic impairment, and death (Benitz et al., 2016; Clyman & Benitz, 2019; Noori et al., 2009; Rios et al., 2018; Vali et al., 2019; Weisz & McNamara, 2014). Treatment of PDA is variable and can be categorized into four broad options a) conservative, observe and wait for the PDA to close spontaneously; b) pharmacologic management; c) surgical ligation; and d) transcatheter device closure (Vali et al., 2019). Importantly, over 60 randomized control trials comparing PDA treatments have failed to establish causality, or demonstrate tangible reduction of adverse neonatal outcomes such as intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), BPD, and death (El-Khuffash et al., 2019). As such, considerable controversy exists as to whether PDA or treatment thereof contribute directly to adverse neonatal outcomes; or if PDA is simply a common occurrence in this patient population.

Characterization of Preterm Infants

Preterm birth is a major public health concern, impacting roughly 15 million babies per year; of which ~ 1 million die from complications related to preterm birth (WHO, 2018). Infants < 28 weeks gestation represent a formidable burden to the health care system and account for the majority of neonatal morbidity and mortality. The World Health Organization (WHO) defines birth prior to 28 weeks as extremely preterm, from 28 to 31 weeks as very preterm, from 32-36 weeks as moderate-to-late preterm and > 37 weeks term (WHO, 2018). Additionally, preterm infants are conventionally classified by birthweight as described in *Table 1*.

Table 1.

Definition of Preterm Birthweights According to the World Health Organization

Birthweight	Category
< 2500 grams	Low birthweight (LBW)
< 1500 grams	Very low birthweight (VLBW)
< 1000 grams	Extremely low birthweight (ELBW)

Problems of Prematurity

Over the past 30-years, advances in neonatal care including antenatal steroids, surfactant replacement therapy, and gentle ventilation strategies have improved the survival of extremely premature infants (Tracy & Berkelhamer, 2019). These interventions have reduced early deaths from respiratory failure with concomitantly increased morbidities as extremely premature infants 22-25 weeks gestation; who once represented the fringe of viability, are now surviving longer. Consequently, extremely premature infants are more susceptible to developing late-onset sepsis, NEC, BPD, and retinopathy of prematurity (Stoll et al., 2015). Despite improved survival, morbidity including PDA remains high in the extremely preterm infant (Clyman & Benitz, 2019). Current care includes early utilization of non-invasive respiratory support including continuous positive airway pressure or nasal intermittent positive pressure ventilation to reduce respiratory distress, ventilator-induced lung injury, and risk of BPD (Committee on et al., 2014; Jensen, 2019). Despite increased utilization of noninvasive respiratory support, invasive conventional mechanical ventilation continues to be the most common respiratory support modality for premature infants with RDS (Dargaville et al., 2016; Moya et al., 2019). Extremely premature infants are more likely to require both prolonged mechanical ventilation and definitive treatment of the PDA; a combination which is commonly associated with adverse neonatal outcomes, although the precise mechanisms and causal linkage remains to be established.

Pulmonary Consequences of a Hemodynamically Significant PDA

Preterm infants with a moderate-large HsPDA may be exposed to high-volume left-to-right shunt for prolonged periods, resulting in pulmonary over circulation and edema formation; further reducing the low pulmonary compliance related to the RDS disease process (Appendix A). Progressive reductions in respiratory system compliance, coupled with worsened gas

exchange often necessitate escalation of mechanical ventilation support to maintain adequate oxygenation, ventilation, and pH (Giesinger et al., 2019). Therefore, infants with RDS and concurrent HsPDA are at high risk for the development of ventilator-induced lung injury and prolonged duration of mechanical ventilation. Indeed, the inability to liberate preterm infants from mechanical ventilation following the failure of pharmacologic interventions to close the PDA is the primary reason infants are referred for definitive closure of the PDA (Jhaveri et al., 2010; Krishnappa et al., 2019).

In theory, interventions to close the PDA should improve lung compliance and respiratory morbidities; however, there is a paucity of modern data in this area (Gerhardt & Bancalari, 1980; Lehenbauer et al., 2018; Naulty et al., 1978). Moreover, pulmonary function may be negatively impacted by PDA ligation surgery; as thoracotomy, dissection, and instrumentation of the lung and have been associated with complications including pneumothorax, bronchial obstruction, diaphragmatic paresis, and vocal cord paralysis (Vali et al., 2019). Furthermore, in a subset of infants lung compliance remains unchanged or worsens following ligation and may require increased ventilator support (Heuchan et al., 2012; Szymankiewicz et al., 2004). Post-cardiac ligation syndrome (PCLS) complicates 28-45% of all PDA ligations and is characterized by symptoms including systemic hypotension with deficits in oxygenation and ventilation within 6-24 hours following the procedure (Clyman et al., 2014; Harting et al., 2008; Ulrich et al., 2018).

The ability to predict which infants will demonstrate favorable improvements in lung compliance following definitive PDA closure is hampered by difficulties identifying the proportion of respiratory insufficiency that is related to HsPDA versus other risk factors associated with prematurity; mainly, evolving chronic lung disease and prolonged mechanical

ventilation (Krishnappa et al., 2019). While many investigators have described postoperative deficits in oxygenation and ventilation, few have comprehensively described the escalation phase of the ventilation strategy or identified an optimal point to transition to high-frequency ventilation (de Waal et al., 2009).

High-Frequency Ventilation

High-frequency ventilation (HFV) is an alternative form of mechanical ventilation that employs rapid breathing frequencies and delivers tidal volumes that are generally smaller than anatomic dead space (Lampland & Mammel, 2007). HFV is often used as a lung-protective rescue approach when gas exchange deteriorates and infants can no longer be safely supported on conventional mechanical ventilation (Wheeler, Smallwood, O'Donnell, Gagner, & Sola-Visner, 2017). Notably, randomized studies comparing the use of high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV) to conventional mechanical ventilation have not demonstrated significant benefits in neonatal outcomes for elective or rescue usage (Cools et al., 2015; Rojas-Reyes & Orrego-Rojas, 2015). Additionally, these trials were conducted decades ago and excluded extremely premature infants (e.g. 22-25 weeks). Despite the lack of conclusive evidence, HFV is a standard of care for premature infants with 28% to 62% of infants between 22-28 weeks gestation receiving some type of HFV during their stay in neonatal intensive care (Patel et al., 2015; Stoll et al., 2015). However, risk factors associated with conventional mechanical ventilation failure and the subsequent need for rescue HFV have not been adequately described in the setting of PDA. Currently, there are no predictive tools to aid bedside clinicians in deciding if and when HFV should be initiated. Therefore, it is desirable to clearly define the conventional ventilation strategy in relation to the development of respiratory decompensation following interventions to close the PDA.

Metrics of the Severity of Respiratory Illness in Preterm Infants

Historically, the oxygen index: ($OI = \text{mean airway pressure} \times FIO_2 \times 100 / PaO_2$) was utilized to assess the severity of respiratory illness, direct interventions, and evaluate response to therapies such as surfactant, HFV and inhaled nitric oxide (Golombek & Young, 2010; Stewart et al., 1996; Willson et al., 2005). In contemporary practice, umbilical lines are time-limited and the routine placement of peripheral arterial lines in premature infants is infrequent due to small patient size or concerns of infection, thrombosis, iatrogenic anemia, and ischemia (de Brito et al., 2010; Deindl et al., 2018; Shahid et al., 2014). The lack of arterial access precludes infants from the routine calculation of OI and subsequent risk stratification.

Respiratory severity score ($RSS = \text{mean airway pressure} \times FiO_2$) is a validated noninvasive surrogate for OI, used to assess the severity of respiratory failure in premature infants undergoing mechanical ventilation (Malkar et al., 2015). A low RSS denotes less respiratory support, 1.6 has been associated with successful extubation (Mhanna et al., 2017), 3.5 represents more severe lung disease (Ballard et al., 2006) and $RSS \geq 6$ on day of life 30 has been associated with increased mortality and prolonged duration of mechanical ventilation (Malkar et al., 2015).

Statement of the Problem

PDA is a frequent complication in preterm infants with RDS and is inversely proportional to gestational age. While the optimal timing and treatment of PDA remains controversial; the inability to wean from mechanical ventilation is the primary reason infants are referred for surgical or catheter-based interventions to close the PDA. Respiratory decompensation following interventions to close the PDA is a relatively common occurrence in the perioperative management of these infants. The ability to predict escalations in mechanical ventilator settings

is desirable and may allow for timely individualization of the ventilation strategy and improvement in pulmonary outcomes for this fragile patient population.

Purpose of the Research

The purpose of the present study is to: a) describe risk factors associated with failure of conventional mechanical ventilation in premature infants following surgical ligation (SL) or transcatheter PDA closure (TCPC); b) describe phenotypes of preterm infants that are at elevated risk for the development of respiratory decompensation following SL or TCPC and c) describe differences in outcomes, such as requirement for rescue with HFV, need for vasoactive medications, duration of mechanical ventilation, length of stay and morbidity between subjects who had SL and those who underwent TCPC.

Review of the Literature

Overview of Fetal Circulation and the Physiology of Transition

The transition from intrauterine to extrauterine life is characterized by a complex sequence of physiologic adaptations prior to the establishment of post-natal circulation (Deshpande et al., 2018). Fetal lungs do not participate in gas exchange; therefore, the fetus is reliant upon the mother's placenta to provide oxygen and nourishment. Fetal circulation involves a series of three shunts: a) ductus venosus; b) foramen ovale; and c) the ductus arteriosus (Appendix B).

Antenatally, oxygenated blood and nutrients enter the fetal circulation; flowing from the placenta via the umbilical vein to the inferior vena cava and transiting the ductus venosus to the right atrium (RA). The oxygenated blood from the ductus venosus mixes with the deoxygenated venous blood returning to the RA. Approximately two-thirds of this admixture is shunted from the RA through a hole in the septum between the right and left atrium; referred to as the patent foramen ovale (PFO). As such, 90% of the blood entering the PA bypasses pulmonary circulation via the patent ductus arteriosus, with the remaining 10% entering the pulmonary vascular bed (Homma et al., 2016). Further, the hypoxemic fetal environment promotes the production of endogenous prostaglandin E₂ (PGE₂) and prostaglandin I₂ (PGI₂); which maintain ductal patency (Rios et al., 2018).

From the left atrium (LA), oxygenated blood enters the left ventricle (LV) before being pumped into the aorta and systemic circulation. The remaining one-third of blood in the RA is directed to the right ventricle (RV) and subsequently ejected into the pulmonary artery (PA). Importantly, fetal life is characterized by non-participation of the lungs and dependence upon the placenta for gas exchange. In utero, fetal lungs are filled with fluid and have a high pulmonary

vascular resistance (PVR). Two primary factors contribute to high fetal PVR; hypoxic vasoconstriction secondary to low oxygen concentrations in pulmonary blood flow and direct compression of the pulmonary vessels by the mechanism of low lung volumes.

Ductal Patency and Mechanisms of Closure

The onset of ventilation is considered responsible for initiating the physiologic transition from fetal circulation to postnatal circulation (Deshpande et al., 2018). Following the initial series of breaths and the establishment of functional residual capacity, alveolar oxygen content dramatically increases; resulting in a rapid reduction of PVR. The sudden reduction in PVR promotes increased pulmonary blood flow. Moreover, clamping of the umbilical cord and removal of the placenta from the systemic circulation marks a rapid increase in SVR with a concurrent reduction in right-heart preload.

The combination of reduced PVR and increased SVR generally leads to a progressive reversal of blood flow across the PDA, from entirely right-to-left to predominately left-to-right (Rios et al., 2018). At this stage, the PDA is exposed to high systemic arterial oxygen concentration with concurrent reductions in bradykinin production and circulating prostaglandin levels, which are thought to induce vasoconstriction and functional closure of the PDA (Deshpande et al., 2018). In a prospective study, Jain et al. (2014) performed serial echocardiograms during the first 48-hours of life and demonstrated that 96% of term infants had no transductal flow by 40-hours of age; suggestive of functional PDA closure. In contrast, 70% of preterm infants < 28 weeks and 80% of those born at 24-25 weeks gestation failed to have spontaneous closure of the DA within the first 10-days of life (Koch et al., 2006; Madan et al., 2009). Further, Semberova and colleagues (2017) reported that among 280 VLBW infants who underwent conservative management for PDA, 85% had spontaneous closure before hospital

discharge. Therefore, without early treatment to close the DA, a subset of preterm infants will be exposed to systemic left-to-right shunting across the PDA for a period of time, with most PDAs closing spontaneously by 44 weeks postmenstrual age (Slaughter et al., 2019). While the clinical significance and role of this exposure has not been fully elucidated; it is important to consider PDA in context with phases of lung development.

PDA: In Context with Phases of Lung Development

Lung development occurs in four overlapping phases of gestation: a) embryonic period (0-6 weeks); b) pseudoglandular (6-16 weeks); c) canalicular (16-24 weeks) and d) saccular (24-40 weeks). The expansion of pulmonary circulation mirrors each respective lung development stage with capillary and vascular branching, supplying perfusion to the rapidly expanding pulmonary tree. Lung development begins approximately four-weeks following conception with the formation of large airways including the trachea, mainstem bronchi, and initial segments of smaller conducting airways (Schittny, 2017).

The early pseudoglandular phase is characterized by the completion of 20 generations of smaller conducting airways and the first few generations of alveolar ducts (Smith et al., 2010). The canalicular phase represents the development of the pulmonary parenchyma, multiplication of capillaries, and formation of the capillary network around airspaces. Notably, at around 20 weeks of gestation type II alveolar cells appear and are responsible for the synthesis, storage, and secretion of surfactant. Moreover, the two primary developments during the canalicular stage include formation of the air-blood barrier and the beginning of surfactant production (Schittny, 2017). During the saccular stage, the terminal airways grow in length and diameter forming clusters of distal airspaces. The resulting clusters or saccules are defined as the alveolar ducts and alveolar sacs, however, true alveoli do not begin to form until 32-36 weeks (Smith et al.,

2010). The final stage of lung development, alveolarization, is characterized by the formation of mature true alveoli.

Alveoli are thin-walled sacs that enable gas exchange across the capillary membrane; in which, carbon dioxide is removed from the blood, and oxygen is added with each successive breath. The alveoli are comprised of thin, flat, type I epithelial cells which cover 90% of the inner surface, and type II epithelial cells which occupy the remaining 10% (Evans et al., 1973). Alveolarization is the final stage of lung development, which represents the formation of fully functional alveoli and occurs between 36 weeks to 2-years postnatal age (Langston et al., 1984). Alveolarization is thought to be mostly completed between 18-24 months of age (Burri, 2006).

Surfactant

The pulmonary surfactant system is a crucial component to maintaining alveolar expansion and adequate surface area for gas exchange. Surfactant is a lipid that coats the inner surface of the alveoli and reduces surface tension; thereby promoting alveolar stability and preventing alveolar collapse (Orgeig et al., 2015). While the type II epithelial cells are present at 20 weeks gestational age, the quality and production of surfactant is insufficient until around 30 weeks gestation (Smith et al., 2010). It is important to highlight that both lung development and surfactant production are incomplete in extremely preterm infants; as their genesis temporally coincides with the pseudoglandular or canalicular periods. As such, these infants have underdeveloped lungs and surfactant deficiency, with most requiring exogenous surfactant replacement and positive-pressure ventilation.

Respiratory distress syndrome

Respiratory distress syndrome (RDS) is the primary cause of respiratory failure in premature infants, resulting from immature lung development and surfactant deficiency (Stoll et

al., 2015). Historically, surfactant was routinely administered to preterm infants via an endotracheal tube in combination with mechanical ventilation. However, mounting evidence from multicenter randomized control trials and subsequent meta-analyses indicate that nasal continuous positive airway pressure (CPAP) is an effective alternative to intubation and prophylactic surfactant administration (Bahadue & Soll, 2012; Fischer & Buhrer, 2013; Rojas-Reyes et al., 2012). Based upon these data, the American Academy of Pediatrics recommends CPAP utilization immediately after birth for spontaneously breathing infants, with selective surfactant replacement being reserved for infants who subsequently require intubation and mechanical ventilation (Committee on et al., 2014). Therefore, current treatment includes early utilization of CPAP to reduce respiratory distress, ventilator-induced lung injury, and risk of BPD (Committee on et al., 2014; Jensen, 2019).

Despite increased utilization of non-invasive respiratory support, approximately 50% of infants < 28 weeks GA subsequently require intubation and mechanical ventilation, with risk increasing inversely to GA. Moreover, 70% of infants undergo invasive mechanical ventilation preceding the initiation of CPAP in the delivery room (Dargaville et al., 2016; Moya et al., 2019). Therefore, the majority of extremely premature infants require invasive mechanical ventilation. Although mechanical ventilation is a life-saving intervention for preterm infants, it has been associated with increased mortality and development of morbidities including BPD, retinopathy of prematurity, and neurodevelopmental impairment (Chawla et al., 2017). Considering the prevalence of both RDS and PDA are inversely proportional to gestational age, the resultant risk factors are similar to considerable overlap in morbidities.

Management of Mechanical Ventilation in Preterm Infants

The role of mechanical ventilation is to safely support effective gas exchange while minimizing the risk of ventilator-induced lung injury. Preterm infants are most commonly ventilated using pressure-control or volume-targeted modes of ventilation. In pressure-controlled modes, tidal volume (V_T) is variable and peak inspiratory pressure (PIP) is constant; and in volume-targeted ventilation, V_T is set and PIP is variable; both are affected by changes in lung compliance and resistance. Despite the choice in mode, the general aims of the ventilation strategy are to a) prevent alveolar over-distention or volutrauma by controlling V_T in the 4-6 mL/kg range and limiting PIP < 25 cm H₂O; b) titrate positive end-expiratory pressure (PEEP) to reduce the repetitive closing and reopening of alveolar lung units or atelectrauma via recruitment and maintenance of end-expiratory lung volume or functional residual capacity; c) minimize swings in the partial pressure of arterial carbon dioxide (PaCO₂) and blood pH levels; and d) reduce exposure to a high fraction of inspired oxygen (Klingenberg et al., 2017).

Variability in patient size, lung maturity, available equipment, presence of endotracheal tube cuff leak, and the heterogeneous range of acute and chronic diagnoses make the development of a single “ventilator strategy” difficult. Therefore, the mode of ventilation and combination of settings are individualized according to patient characteristics, with considerable variation based upon the underlying condition and institutional preference.

Mechanical ventilation strategies can influence blood flow through the PDA. A review of how mechanical ventilation is used in the perioperative management of single-ventricle physiology, such as hypoplastic left heart syndrome (HLHS) illustrates this relationship. Unlike a structurally normal heart where blood flow is supplied in series and managed by two ventricles (right and left), the infant with HLHS is dependent upon a single right ventricle. In single-

ventricle physiology, cardiac output is supplied in parallel with blood flow being divided between both pulmonary and systemic circuits (Rossano & Chang, 2006). These infants are reliant on the PDA to provide systemic perfusion (right-to-left shunt). The distribution of pulmonary blood flow (Q_p) and systemic blood flow (Q_s) is directly influenced by resistance in the pulmonary and systemic circulation; which are considered to be balanced when the $Q_p: Q_s$ ratio equals ~1:1 (Barnea et al., 1994). The gradual reduction in PVR after the first few days of life leads to an imbalance or over circulation of the pulmonary circuit with concomitant hypoperfusion of the systemic circulation; increased Q_p and decreased Q_s . Mechanical ventilation strategies to increase PVR include a) low fraction of inspired oxygen ($FiO_2 \sim 0.21$ - 0.25); b) permissive hypercapnia; and c) increased mean airway pressure. Collectively, these strategies can be utilized for infants with HsPDA to increase PVR to reduce DA shunt volume.

The pulmonary vasculature is responsive to both hypoxia and acidosis; both of which can be manipulated during invasive mechanical ventilation to induce vasoconstriction and increase PVR. Permissive hypercapnia refers to purposely allowing the partial pressure of carbon dioxide (PCO_2) in the blood to exceed normal physiologic limits (e.g. > 45 mm Hg). Carbon dioxide exerts opposing effects on the pulmonary and systemic vasculature; with hypercapnia resulting in pulmonary vasoconstriction and systemic vasodilation (Smith et al., 2018). The proposed benefits of hypercapnia in premature infants is to minimize the risks of mechanical ventilation to reduce lung injury and neurologic damage. However, a meta-analysis of 4 randomized control trials failed to demonstrate efficacy in reducing BPD, ROP, NEC, IVH, or neurodevelopmental outcomes of extremely low birth weight infants (Ma & Ye, 2016). Nevertheless, permissive hypercapnia is commonly utilized in the management of preterm infants undergoing mechanical ventilation. While the physiologic basis of utilizing hypercapnia to induce pulmonary

vasoconstriction is sound, there have been no studies to date investigating the impact of permissive hypercapnia on HsPDA (Smith et al., 2018).

Mean airway pressure (\bar{P}_{aw}) is calculated as: $\bar{P}_{aw} = (PIP - PEEP) \times T_I/T_{total} + PEEP$; where T_I is inspiratory time and T_{total} is total respiratory cycle time (Hess, 2014). Small observational studies have evaluated the efficacy of lung recruitment using higher levels of PEEP or mean airway pressure on pulmonary, systemic, and ductal blood flow (de Waal et al., 2009; de Waal et al., 2007). Fajardo et al, compared PEEP levels of 5 and 8 cmH₂O in preterm infants with PDA and found that mild reductions in left-to-right shunt through the DA was associated with PEEP of 8 cmH₂O and without impairment of cerebral oxygenation and perfusion (Fajardo et al., 2014) In contrast, de Waal and colleagues prospectively studied the effect of lung recruitment in a cohort of mostly premature infants receiving HFOV and found no significant differences in ductal shunting when comparing a \bar{P}_{aw} of 8 cmH₂O to 20 cmH₂O (de Waal et al., 2009). \bar{P}_{aw} is a frequently monitored parameter in infants undergoing mechanical ventilation which can be used to characterize the level of ventilator support and has been factored into several indices for stratification of respiratory illness severity; including the OI, RSS, and oxygen saturation index. For example, infants who are ready to be liberated from mechanical ventilation typically have $\bar{P}_{aw} < 10$ cm H₂O; whereas, infants with moderate-severe respiratory failure \bar{P}_{aw} often exceed 15 cm H₂O.

Treatment of PDA

Despite decades of research, including over 65 randomized control trials, the optimal management strategy for PDA remains highly controversial; as none of the current treatment strategies have demonstrated tangible improvements in the outcomes of premature infants with PDA (Smith & El-Khuffash, 2020). This lack of consensus is underscored in a recent survey that

compared the management strategies for PDA in premature infants in the United States.

Sathanandam et al. (2019) found that 80% of cardiologists believed that PDA closure impacts preterm morbidity and mortality as compared to 54% of neonatologists ($p < .001$). Neonatologists preferred conservative management, whereas cardiologists favored interventions to close the PDA (77% vs. 95%, $p < .001$). While the timing and method of closure was variable between groups, over 60% of both groups agreed that HsPDA in preterm infants warranted treatment.

Hemodynamically Significant Patent Ductus Arteriosus

The term “hemodynamically significant PDA” or HsPDA is frequently used to differentiate between a small PDA which may have little impact on circulation, from a symptomatic (high shunt volume) PDA which is likely to result in systemic hypotension. Therefore, PDA can be conceptualized on a continuum ranging from supportive to pathologic, taken in context with gestational age. In infants with complex congenital heart disease, maintaining ductal patency is imperative to supplying either pulmonary (e.g. pulmonary atresia, Ebstein’s anomaly) or systemic circulations (e.g. coarctation of the aorta, hypoplastic left heart syndrome) to prevent congestive heart failure until surgical repair can be performed. Additionally, maintaining ductal patency in infants with acute pulmonary hypertension can also be supportive, as the PDA permits right-to-left flow in the setting of systemic RV pressures and RV dysfunction.

In preterm infants without congenital heart disease or pulmonary hypertension, the PDA evaluation can be subdivided into either physiologic or pathologic manifestations. For infants with physiologic PDA, there is minimal impact on cardiovascular stability; whereas, a pathologic PDA contributes directly to hemodynamic instability (Rios et al., 2018). Therefore, optimal

management of PDA must be individualized based on whether the PDA is physiologic or pathologic.

Classic clinical symptoms of the HsPDA include tachycardia, cardiac murmur, hyperactive precordium, bounding pulses, and widened pulse pressure. Moreover, HsPDA may be suspected based on radiographic observation of increased pulmonary congestion and cardiomegaly in context with the need for escalation of mechanical ventilation settings or difficulty weaning from mechanical ventilation (Su et al., 2020). However, these findings lack specificity and cannot accurately diagnose if the PDA is pathologic. Therefore, the widespread use of serial transthoracic echocardiography (TTE) has provided significant insight into the clinical evaluation of ductal shunting and quantification of HsPDA.

The assessment of HsPDA is multifactorial and represents a complex interaction between several intrinsic and extrinsic factors (Appendix C). Unfortunately, there is no universal definition of HsPDA to guide clinicians in determining whether the DA requires intervention or will close spontaneously. Many trials have utilized arbitrary cut-offs based on PDA size, which may not fully account for the underlying pathologic consequences or resultant short and long-term outcomes related to HsPDA (El-Khuffash et al., 2019). According to El-Khuffash, Levy, Gorenflo & Frantz (2019) several factors including a) the influence of PDA shunt volume on pulmonary and systemic circulation; b) myocardial function; and c) perinatal characteristics which may modify or exacerbate pathologic consequences of the shunt must be considered. Indeed, assessment of shunt volume rather than measurements of PDA size afford a more complete appraisal of the hemodynamic impact of the PDA.

Quantification of blood flow in the cardiovascular system is derived from Ohm's Law as applied to hydraulic systems, where blood flow (Q) is equal to the pressure gradient (ΔP) divided

by vascular resistance (R_v) as denoted by the equation: $Q = \frac{\Delta P}{R_v}$ (Gerrah et al., 2017). Velocity (u) is a clinically relevant parameter in the assessment of cardiovascular performance. Increased velocity is often associated with pathology; with a PDA this can be appreciated during auscultation as a cardiac murmur representing flow turbulence through the PDA. Blood flow across the PDA is governed by Poiseuille's Law which describes the relationship between transductal pressure gradients, diameter, length, and viscosity (Appendix D). Notably, vessel diameter (d^4) corresponds to a fourth-order relationship with flow; where small changes in vessel size have a dominant impact on flow dynamics. The Bernoulli Principle (Appendix D) expresses the relationship between flow, velocity, and pressure. During peak systole, blood flow from the aorta (high-pressure) transits the PDA (smaller diameter) before entering the pulmonary artery (larger diameter, lower pressure). As such, the pressure drop across the PDA results in conversion of high-pressure low-velocity flow to low-pressure high-velocity flow; resulting in a pressure gradient between the aorta and pulmonary artery (Gerrah et al., 2017). Importantly, the diameter, length, blood viscosity, transductal pressure gradients and flow across the PDA all change considerably in the first few days of life (de Freitas Martins et al., 2018). Therefore, ductal blood flow is dependent upon downstream resistance and other factors such as a) PDA size in diameter; b) the pressure difference between the aorta and pulmonary artery; c) runoff during diastole; d) turbulence and e) the Venturi effect with smaller restrictive PDAs; increased velocity with subsequent decrease in pressure. Clinically, these principles are incorporated into patient assessment using Doppler echocardiography to quantify pressure gradients, shunt volume, and hemodynamic significance.

Assessment of echocardiographic markers of PDA pathology and hemodynamic significance has become the standard of care in neonatal intensive care units (El-Khuffash &

McNamara, 2017). The intricate relationship between HsPDA; mainly magnitude and duration of exposure to ductal shunt has been associated with reduced lung compliance and may potentially expedite the inflammatory process leading to chronic lung disease (Clyman et al., 2020; Schena et al., 2015). Moreover, the runoff or diastolic “steal” phenomenon occurs when blood moves from vessels of high-pressure such as the aorta to those with lower pressures including the pulmonary circuit. This concept is exemplified by flow reversal during diastole in the descending aorta, which is commonly observed via TTE in infants with HsPDA.

Therefore, it is desirable to identify HsPDA early to determine which infants can be conservatively managed from high-risk infants that require prompt interventional management (e.g. < 26 weeks). El-Khuffash and colleagues (2015) comprehensively examined echocardiographic and physiologic characteristics of infants < 29 weeks gestation using an observational multicenter prospective design. The cohort was divided based upon the binary outcome; presence or absence of chronic lung disease (CLD). Univariate and multivariable logistic regression analyses were performed to identify independent predictors of CLD and death before discharge. These authors identified gestational age, PDA diameter, maximum flow velocity, LV output (a marker of shunt volume and over circulation), and LV a’ wave (a measure of LV diastolic function) on day of life two as independent predictors of CLD and death. From these data, a clinical scoring system was derived, ranging from 0 (low-risk) to 13 (high-risk). The model demonstrated excellent predictive capability with an area under the receiver operating characteristic curve (AUC) of 0.92 (95% CI 0.86-0.97, $p < 0.001$). Infants who ultimately developed chronic lung disease or death had higher scores with a cut-off score of 5 being predictive of CLD or death; sensitivity and specificity of 92% and 87% respectively. It is

important to underscore that the mechanical ventilation strategy also has significant impact on the development of CLD.

PDA Treatment Modalities

The need for PDA treatment continues to be a contentious topic given the high rate of spontaneous closure, evidence of moderate efficacy for pharmacologic treatment, and concerns that iatrogenic effects related to treatment may outweigh benefits. Historically, all PDAs were treated early with either pharmacologic or surgical intervention without assessment of hemodynamic impact. Over time, mounting evidence of adverse neonatal outcomes related to PDA management has led to skepticism about universal treatment; as this approach unnecessarily exposes some infants to potential harm (Lee, 2019). Therefore, trends in management have become more conservative, with decision to treat being deferred and re-evaluated based on the risks/benefit profile of each individual patient. Treatment modalities for PDA can be separated into four options: 1) Conservative management; 2) Pharmacologic therapy; 3) SL and 4) TCPC. The relative advantages and disadvantages of each modality is summarized in (Table 2.).

Table 2.

A Comparison of Treatment Options for HsPDA

Pharmacologic	SL	TCPC
Advantages: <ul style="list-style-type: none"> • Non-invasive • Efficacy 50-70% • May take days to be effective 	Advantages: <ul style="list-style-type: none"> • Efficacy 100% • Immediate and definitive closure 	Advantages: <ul style="list-style-type: none"> • Minimally-Invasive • Efficacy 100% • Immediate and definitive closure
Disadvantages: <ul style="list-style-type: none"> • Renal impairment, oliguria, proteinuria, hyperkalemia • Reduced effectiveness for ELBW infants • White-matter damage • Impaired cerebral perfusion • NEC, SIP • Platelet dysfunction 	Disadvantages: <ul style="list-style-type: none"> • Post-Cardiac Ligation Syndrome (30%) • Vocal cord dysfunction (30%) • Impaired neurodevelopmental outcomes • Surgical complications^a • Cardiorespiratory failure 	Disadvantages: <ul style="list-style-type: none"> • Vascular access complications (1%) • LPA stenosis (1%) • AA stenosis (1%) • Device embolization (1%) • TV damage or regurgitation • Exposure to radiation and contrast • Hypothermia

Note. ELBW = extremely low birthweight infant, NEC = necrotizing enterocolitis, SIP = spontaneous intestinal perforation, LPA = left pulmonary artery, AA = aortic arch, TV = tricuspid valve. *Reprinted with permission from “PDA Closure in ELBW: If, When, and How to do it” by S. Whiting, and S. Sathanandam, 2019, *Update on Critical Issues on Infant and Neonatal Care*, p. 5. Copyright 2019 by IntechOpen.

^aSurgical complications include chylothorax, pneumothorax, diaphragmatic paralysis, vocal cord paresis, bleeding and scoliosis.

Conservative Treatment

Conservative treatment is contingent upon the possibility of the DA closing naturally without treatment. Conservative treatment is an umbrella term for the combination of several non-pharmacologic strategies aimed at decreasing the magnitude of left-to-right shunt via the PDA. As previously mentioned, mechanical ventilation strategies using higher levels of PEEP, permissive hypercapnia, and lower FiO₂ are often utilized to increase PVR with the goal of reducing shunt volume. Additionally, fluid restriction (≤ 130 mL/kg/day) to minimize left-heart loading, targeting higher hematocrit levels 35-40% (to increase viscosity) and diuresis may be considered to mitigate pulmonary edema formation (Smith et al., 2018).

Pharmacologic treatment

Pharmacotherapeutic agents, mainly non-steroidal anti-inflammatory drugs (NSAIDS) such as indomethacin and ibuprofen or non-aspirin pain reliever (acetaminophen) have been used as first-line therapies to close PDA. The administration of NSAIDS or acetaminophen inhibits cyclo-oxygenase enzyme, resulting in downregulation of PGE₂, a potent vasodilator that potentiates ductal patency. Several treatment strategies have been investigated including a) prophylaxis, where all infants are treated early within the first few hours of life; b) early symptomatic, where infants with HsPDA receive NSAIDS between 2-5 days of life; and c) late-symptomatic, where infants with HsPDA receive treatment between 10-14 days of life (Heuchan & Clyman, 2014). Despite over 60 RCTs focusing solely on pharmacologic management, the efficacy, timing, optimal dosing, and safety profiles of these drugs remain incomplete (Marconi et al., 2019). Recent meta-analysis of these studies suggests failure rates of 0.24, 95% CI [0.20, 0.29] for indomethacin; 0.18 [0.14, 0.22] for ibuprofen; 0.19 [0.09, 0.30] for acetaminophen; and 0.59 [0.48, 0.69] for control (no treatment), respectively (Marconi et al., 2019).

Notably, the survival rate of infants born at 23 weeks gestation has improved due to advances in neonatal medicine. Dani and colleagues (2019) performed a multicenter retrospective analysis including infants with HsPDA born between 23-28 weeks gestation. These authors found that HsPDA occurred in 70% of infants born at 23-24 weeks gestation vs. 59% of infants born between 25-28 weeks (Dani et al., 2019). Moreover, failure of the first treatment cycle and subsequent need for SL were significantly higher among the 23-24 week group when compared to infants born between 25-28 weeks gestational age (69% vs. 40%; $p < .001$) and (19% vs. 10%; $p = .011$), respectively.

Surgical Ligation

Surgical ligation of the PDA is performed when pharmacologic treatment is not successful or contraindicated in the setting of NEC, decreased urine output, or elevated risk for bleeding (Lee, 2019). SL is achieved by placing a clip or ligature around the PDA, resulting in immediate closure (Appendix E). The invasive nature of the procedure itself may negatively alter pulmonary function as it requires thoracotomy, retraction of the ribs, dissection, and instrumentation of the lung to provide access to the DA. Moreover, SL is associated with complications including pneumothorax, bronchial obstruction, diaphragmatic paresis, vocal cord paralysis, and scoliosis (Vali et al., 2019). Overall, mortality following SL is low; however, between 28-45% of all PDA ligations are complicated by post-cardiac ligation syndrome (Giesinger et al., 2019; Harting et al., 2008; Ulrich et al., 2018).

Post-cardiac ligation syndrome (PCLS) is a phenomenon characterized by systemic hypotension and deficits in ventilation and/or oxygenation during the 6-24 hour period following SL (Giesinger et al., 2019). PLCS or low cardiac output syndrome occurs secondary to sudden, drastic changes of the loading condition on the left side of the heart following the abrupt closure of the PDA (McNamara et al., 2010; Nealon et al., 2019; Noori et al., 2007). The mechanisms of PLCS are complex and incorporate respiratory decompensation, myocardial dysfunction, and vascular tone dysregulation (Noori & Kumar, 2017). PLCS has been defined as a composite outcome of the need for inotropic agents and oxygenation failure and/or ventilation failure in the absence of any other surgery-related etiology, such as hypovolemia, sepsis, pneumothorax, and chylothorax (Jain et al., 2012; Ulrich et al., 2018). A schematic of factors contributing to PCLS is displayed in (Appendix E).

Transcatheter PDA Closure

The recognition of potential risks of SL has led to the exploration of an alternative minimally invasive, approaches to close the PDA (Backes et al., 2019). Catheter-based closure of the PDA is among the safest of interventional cardiac procedures and is considered the procedure of choice for PDA closure in infants > 5 kg (Backes et al., 2016; Lam et al., 2015). In recent years, devices suitable to “plug” the PDA of premature infants (including extremely low birth weight, <1000 g) have become available and several trials have demonstrated successful and safe TCPC in this population (Backes et al., 2017). The Amplatzer Piccolo™ Occluder Device is one of these devices and is a percutaneous, transcatheter occlusion device intended for the nonsurgical closure of a PDA. The device was approved for infants > 700 grams by the Food and Drug Administration in January 2019 and the first Piccolo device was placed at Boston Children’s Hospital in May 2019.

The Amplatzer Piccolo™ Occluder is a self-expanding, nitinol mesh occlusion device for use in infants to close the PDA. Device configuration consists of a central waist with two retention discs and is configured specifically for PDA morphologies encountered in ELBW infants. In addition to the device’s small size and adjustable profile, the approach for implantation of this device in ELBW infants differs from larger infants (e.g. > 5 kg). In larger infants, the combination of femoral arterial and venous access is performed in the catheterization laboratory to guide and adjust device placement. In infants < 2 kg, arterial access is generally avoided due to the potential for vascular insufficiency and limb loss (Alexander et al., 2016; Backes et al., 2016). Therefore, to minimize the risk of vascular damage, an alternate approach is employed in smaller infants using venous access with a combination of echocardiographic and fluoroscopic guidance to position and deploy the device (Appendix F).

Respiratory Decompensation Review

Several investigators have compared SL to TCPC and found improvement in respiratory morbidity including shorter duration of ventilation, less severe respiratory compromise, more rapid return to baseline respiratory status, and shorter length of stay (Hazeem et al., 2013; Regan et al., 2020; Rodriguez-Ogando et al., 2018; Sathanandam et al., 2018; Balduf, et al., 2019) and lower incidence of PCLS (Serrano et al., 2020). These findings contribute to the emerging body of literature suggesting that occluding PDA via TCPC may result in less postprocedural cardiorespiratory compromise and improvement in short-term outcomes when compared with SL (Appendix G).

Except for Regan (2020) the above investigations included single-center, retrospective designs with small sample sizes. First, the nonrandomized nature of these investigations was reliant on the accuracy of the medical record and may have introduced bias (selection, historical, measurement) or unmeasured covariates. To address the concerns of analyzing retrospective data, two of the largest studies used propensity score matching to balance groups based on gestational age and weight; both of which are known confounding variables in preterm infants (Regan et al., 2020; Sathanandam et al., 2018; Balduf, et al., 2019). Propensity score matching aims to balance treatment groups concerning baseline covariates to reduce selection bias and other potential confounding variables; hence, allowing for a more even comparison of treatment effect (Staffa & Zurakowski, 2018).

Second, the study by Serrano et al. (2020) suggests extremely preterm infants are less likely to develop PCLS following TCPC when compared with their SLC counterparts (20 % vs. 0 %, $p = .016$). These findings must be interpreted with caution as no *a priori* power analysis was performed and hemodynamic support was considered a binary outcome representing the receipt

of hydrocortisone, dopamine, and epinephrine. Moreover, the decision to initiate hemodynamic support was not protocolized and at the discretion of the attending physician. As such, the incidence of post-ligation cardiac syndrome following TCPC remains largely unknown and warrants further investigation.

Third, the timing of intervention may have an important impact on the development of pulmonary comorbidities. Sathanandam and colleagues (2018) used Kaplan-Meier estimates to compare the decline of RSS over time until freedom from $RSS \geq 1$ (minimal ventilator support) occurred. These authors found that late repair (> 8 weeks of age) and elevated pulmonary pressure ($\geq 75\%$ of systolic blood pressure) were independently associated with prolonged (>30 days) elevation of $RSS \geq 1$; $OR = 5.4$, 95% CI [2.2, 9.4], $P < 0.01$ and $OR = 2.86$, 95% CI [1.5, 4.2], $p < 0.05$, respectfully. These findings suggest that earlier closure may confer benefit by avoidance of higher pulmonary artery pressures resultant from prolonged high-volume shunt and progressive development of pulmonary vascular disease. Moreover, early TCPC resulted in a 3-fold reduction in $RSS \geq 1$, which equates to a shorter duration of mechanical ventilation. Further, these findings are in line with other studies that found associations between duration of PDA exposure and the development of BPD (Clyman & Hills, 2020; Clyman et al., 2020; Mirza et al., 2019; Schena et al., 2015).

Last, all studies directly comparing SL to TCPC reported either validated composite scores of respiratory disease severity (Pulmonary score or RSS) or components thereof, such as \bar{P}_{aw} and FiO_2 . While these scores are helpful to quantify the level of ventilator support and oxygen requirement, other important components of the mechanical ventilation strategy such as peak inspiratory pressure, tidal volume, PEEP, and the threshold for the transition to HFV remain largely unexplored. For example, Serrano et al. (2020) reported that 20% of the surgical

group received HFOV prior to surgery, however, \bar{P}_{aw} and FiO_2 requirements were not statistically different between groups at baseline. HFOV was treated as a categorical variable, which resulted in data loss as no pressure amplitude or set frequency were reported. The use of categorical variables rather than actual ventilator parameters makes it difficult for the reader to compare ventilation strategies between groups (aside from \bar{P}_{aw} or FiO_2) as no subjects in the TCPC group required HFOV. Collectively, all of the aforementioned investigations comparing SL to TCPC focused on similar primary or secondary outcomes but did not provide granular data insofar as ventilator parameter changes over time, ventilation and oxygenation goals, or use of clinical practice guidelines.

Given the current lack of equipoise on PDA treatment, these studies represent a pragmatic attempt to define risk factors, operationalize outcome definitions, and inform the development of future randomized control trials. Large multicenter randomized control trials are needed to answer whether a) TCPC represents a more efficacious method of definitive closure than SLC; b) what is the optimal timing for repair; c) whether TCPC is more beneficial on short and long-term outcomes; and d) if TCPC represents an economic improvement over surgery or conservative management.

In the absence of randomized control studies, retrospective and prospective database studies are essential to characterizing high-risk subgroups of infants such as those requiring HFV during the perioperative period. Therefore, it is desirable to clearly define the conventional ventilation strategy employed in relation to the development of respiratory decompensation following definitive interventions to close the PDA with the aim of early identification of high-risk phenotypes. Furthermore, we sought to investigate temporal changes in mechanical

ventilation settings in the first 24-hours following PDA closure to characterize when and which phenotypes of infants are likely to require HFV.

Methods

This chapter details the methodology used for the present study and is subdivided into the following sections: research design, participants and population, inclusion criteria, exclusion criteria, data collection, measurements, and data analysis.

Research Design

The present study is a single-institution, retrospective review of the electronic medical record. A descriptive research design was chosen because there are no previous investigations examining the escalation phase of mechanical ventilation following definitive PDA closure between SL and TCPC. The primary outcome of interest was a 50% increase in RSS above pre-procedure value within 24-hours following SL or TCPC was selected based upon our perception of clinically significant escalation of FiO₂ or mechanical ventilation support.

Participants and Population

All participants were born at outside facilities and transferred to Boston Children's Hospital Neonatal Intensive Care Unit (NICU) for further management of the PDA. Subjects were identified from a clinical registry database maintained by the Neonatal Intensive Care Unit at Boston Children's Hospital. A retrospective analysis of infants admitted to the NICU between January 2014 and October 2020, qualified for expedited review and was approved by the Institutional Review Board (IRB #P00035857).

Inclusion Criteria

Enrolled participants were < 37 weeks gestational age and underwent invasive mechanical ventilation before and after interventions to close the PDA and received SL or TCPC of the PDA at Boston Children's Hospital between January 2014- October 2020.

Exclusion Criteria

Infants with a) major congenital heart disease (aside from septal defects); b) known genetic or significant congenital anomalies; c) infants on non-invasive mechanical ventilation; and d) infants who did not undergo definitive PDA closure were excluded.

Data Collection

Demographic information and perinatal factors were collected from the medical record of each participant including gestational age, birth weight, mode of delivery, Apgar scores, gender, race, ethnicity, and postmenstrual age upon admission. Echocardiographic markers of HsPDA including the presence or absence of left-to-right flow through the PDA, PDA diameter, peak transductal gradient during systole, LA dilation, LV dilation, and diastolic flow reversal in the abdominal aorta were obtained from pre-procedure echocardiography reports. Additionally, clinical information such as maternal risk factors, antenatal and postnatal steroid administration, surfactant replacement therapy, culture-proven sepsis, and duration of mechanical ventilation prior to transfer and duration of PDA exposure were obtained. Ventilator parameters, physiologic variables, and clinical characteristics were extracted from the electronic medical record at admission, pre-procedure, post-procedure, and 6, 12, and 24-hours post-procedure. As a standard of care, infants are managed with conventional ventilation during SL and TCPC procedure. High-frequency jet ventilation and high-frequency oscillatory ventilation are reserved for rescue therapy in the setting of refractory hypercapnia or hypoxia and have been described in previous publications (Wheeler et al., 2017; Wheeler et al., 2020). We routinely set HFOV frequency at 15 Hz for preterm infants and maintain inspiratory-expiratory ratio of 1:2.

All PDA ligations were performed in the operating room by pediatric cardiothoracic surgeons. Surgical ligation was accomplished via left thoracotomy and placement of a clip or

ligature on the DA. All TCPC procedures were performed in the cardiac catheterization suites by interventional cardiology. Access was achieved via ultra-sound guidance into the femoral vein and advancement of the catheter into the ductus under fluoroscopy. Echocardiography and angiography were used to derive measurements for device selection and ensure proper positioning of the device within the DA.

All data were entered into a clinical registry database for preterm infants who underwent definitive PDA closure created in REDCap (Vanderbilt University, Nashville, TN). Briefly, REdCap (Research Electronic Data Capture) is a website that securely manages HIPAA-sensitive information and is available to researchers affiliated with Boston Children's Hospital. Several data abstraction instruments were created within REDCap and subsequently utilized to organize data according to the flow of information within electronic medical records (PowerChart, Cerner Corporation, North Kansas City, MO). Before data collection, each variable was operationally defined using specified criteria with a simplified response section and specific data quality rules assigned to each field. Protocols for abstraction were used to facilitate proper coding of variables and assist chart reviewers with data collection. All data were internally linked to the records using the medical record number (MRN) and subject ID number. A master code was created and stored separately from the coded data set on HIPAA-compliant electronic systems that meet the standards for protected health information established by Boston Children's Hospital. Data was de-identified of all protected health information before statistical analysis.

Measurements

Measurements included mechanical ventilator setting, monitored physiologic parameters, laboratory values, and calculation of \bar{P}_{aw} and RSS. Serial measurements were obtained over six

epochs: admission to the NICU, pre-procedure, post-procedure, and at 6, 12, and 24-hours post-procedure. Mechanical ventilation, laboratory, and physiologic data were recorded every hour in the electronic medical record, and values were abstracted to reflect reported values nearest the event of interest (e.g. pre-procedure or post-procedure). Laboratory values were included for analysis provided they were reported within 1-hour, before or after the time frame of interest.

Mean airway pressure

$$\text{Mean airway pressure } \bar{P}_{aw} = [(PIP - PEEP) \times T_I/T_{total}] + PEEP$$

Where PIP is peak inspiratory pressure (cm H₂O); PEEP is positive end-expiratory pressure (cm H₂O); T_I is inspiratory time (seconds) and T_{total} is total respiratory cycle time in one minute (Hess, 2014). Observed measurements of \bar{P}_{aw} are routinely recorded as monitored parameters during mechanical ventilation and were subsequently used to calculate Respiratory Severity Score.

Respiratory Severity Score

Respiratory Severity Score (RSS) = [mean airway pressure x FiO₂] is a validated non-invasive metric used to assess the severity of respiratory failure in premature infants undergoing mechanical ventilation (Malkar et al., 2015). There is a strong linear correlation between OI and RSS ($r^2 = 0.982$) when oxygen saturation (SpO₂) is between 88% and 94% (Iyer & Mhanna, 2013); which is the standard oxygen saturation range in the Neonatal Intensive Care Unit at Boston Children's Hospital. As such, we utilized RSS to monitor and trend the severity of respiratory illness in preterm subjects who underwent SL or TCPC.

Outcomes

Our primary outcome of interest was Respiratory Decompensation; operationally defined as a 50% increase in RSS above pre-procedure value within 24-hours following DA ligation or

device closure. Secondary outcomes included a) Oxygenation failure defined as an increase in \bar{P}_{aw} (cm H₂O) or FiO₂ by 20% of pre-ligation baseline for ≥ 1 -hour in the 24-hour period immediately following SL or TCPC; b) Ventilation failure defined as an escalation to HFV or increase of HFJV peak inspiratory pressure or HFOV ΔP by 20% for ≥ 1 -hour in the 24-hour period immediately following SL or TCPC; c) Hypotension defined as the need to initiate a new vasoactive agent or an increase in dose 20% of pre-ligation baseline for ≥ 1 -hour; and d) Post-Ligation Cardiac Syndrome: defined as the combination of hypotension, oxygenation failure and ventilation failure (Jain et al., 2012). Further, all-cause mortality during ICU admission, ICU length of stay (days), and reported prevalence of morbidities such as IVH, BPD, ROP, and NEC were assessed.

Data Cleaning

Clinical data, particularly data sets which were collected retrospectively are prone to error and incompleteness given the systematic variation in which the data were collected and entered by healthcare professionals (Idri et al., 2018). To mitigate potential issues with data quality, the complete data set was reviewed for outliers, missing data, and errors before analysis. To evaluate for errors within the dataset, descriptive statistics including frequencies and ranges for all variables were reviewed. Minimum and maximum ranges were used to assess both physiologic plausibility of continuous variables and proper coding of categorical variables (Pallant, 2010). The application of data preprocessing (cleaning) to medical datasets has been shown to improve both clinical interpretation and performance of predictor variables (Mendes et al., 2015; Titapiccolo et al., 2012).

Data Analysis

The cohort was divided based upon repair type; TCPC and SL (analysis 1). A secondary analysis was performed to assess for differences between subjects who required post-procedural

HFV and those who remained on conventional ventilation. For the secondary analysis, the cohort was divided based on whether the subjects underwent post-procedural HFV and compared with the cohort who continued to receive conventional ventilation (analysis 2). Descriptive statistics were used to characterize the sample and assess the distribution of continuous variables (e.g. skewness and kurtosis). Normality of data was assessed using the “Explore” command in SPSS, which allows for data visualization (e.g. histograms and Q-Q plots) and analysis of normality using the Kolmogorov-Smirnov and Wilk-Shapiro tests (Pallant, 2010). For normally distributed data, continuous variables were summarized using means and standard deviations and compared using an unpaired t-test. Non-normal distributions are described using median (*Mdn*) and interquartile range (*IQR*) and compared using the Mann Whitney *U*-test. Categorical variables were summarized using frequencies, percent’s and proportions and compared using chi-square or Fisher’s exact test as appropriate. The Holm-Sidak procedure was used to account for multiple comparisons and to preserve type 1 error rate via multiplicity adjusted *P* values (Staffa & Zurakowski, 2020). Data analysis was performed with SPSS Statistics 24 (IBM, Armonk, NY) and Prism (GraphPad version 8, La Jolla, CA). All tests were two-sided and *P* values <.05 were considered significant.

Results and Findings

A total of 168 infants who underwent definitive PDA closure were identified, of which 110 subjects were eligible for the study (Appendix H). All subjects were referred for PDA closure following the failure of or contraindications to pharmacologic treatment. The presence of PDA was confirmed by echocardiography in all participants within 2-days of definitive intervention. There was a 4:1 ratio of infants who underwent SL ($n = 88$) to TCPC ($n = 22$). Subjects in both groups were similar for sex, gestational age, birth weight, and other perinatal factors (Appendix I). Infants in the TCPC group were older at the time of the procedure and underwent mechanical ventilation for twice as many days prior to referral. Additionally, the TCPC group had a larger ductal diameter, longer duration of exposure to HsPDA, and higher prevalence of left ventricle dilation via echocardiogram.

Table 5.

Mechanical Ventilation and Physiologic Variables Upon Admission

Variable	SL ($n = 88$)	TCPC ($n = 22$)	<i>P</i> value
CMV PIP, cm H ₂ O	20 (18-23)	24 (21-26)	.018*
V _T , mL/kg	6.5 (6-8)	7 (6-9)	.68
<i>f</i> , breaths/min	31 (28-40)	30 (26-35)	.56
PEEP, cm H ₂ O	6 (5-6)	7 (7-8.5)	.006**
FiO ₂	.4 (.30-.6)	.4 (.40-.93)	.22
pH	7.23 (7.17-7.28)	7.32 (7.25-7.37)	.006**
PCO ₂ , mm Hg	63 (55-72)	60 (46-71)	.76
HFV	14 (16%)	4 (18%)	.97

Note. CMV PIP = conventional mechanical ventilation peak inspiratory pressure, V_T = exhaled tidal volume, PEEP = positive end-expiratory pressure, *f* = set respiratory rate, SpO₂ = oxygen saturation, PCO₂ = partial pressure of carbon dioxide via blood gas, HFV = high-frequency ventilation. * $p < .05$. ** $p < .01$.

Mechanical Ventilation and Physiologic Variables at NICU admission

Several differences in mechanical ventilation parameters and physiologic data were observed between groups at NICU admission. Subjects in the TCPC group exhibited higher median RSS 5.4 *IQR* (4-13) vs. 3.8 *IQR* (3-6), $p = .024$ and \bar{P}_{aw} 13 cm H₂O *IQR* (11-15) vs. 10 cm H₂O *IQR* (8-11), $p = .006$, respectively. Median PEEP, PIP, and pH were also higher in TCPC group. HFV requirement and other respiratory variables were similar at admission between groups and are displayed in (Table 5).

Assessment of Post-procedural Respiratory and Cardiovascular Outcomes

Our primary outcome of interest, an increase in RSS > 50 % above pre-procedural values was similar between groups at post-procedure and 6-hours. Twelve-hours after closure of the DA, 40% of the SL group demonstrated RSS > 50% above pre-procedural values, compared with 3% of the TCPC group ($p = .021$). No differences were observed between groups for secondary outcomes including PIP > 20%, \bar{P}_{aw} >20%, FiO₂ >20%, hypotension and PCLS. Post-procedural outcomes data are presented in Table 6.

Analysis 1: Comparison of Post-procedural Respiratory Decompensation

The TCPC group was characterized by elevated PEEP during all measurements from NICU admission to 24-hours. \bar{P}_{aw} was higher in the TCPC group from admission through 12-hours post-procedure. Moreover, elevated RSS and FiO₂ persisted in the TCPC group from admission to post-procedural measurements and were similar to the surgical group for all subsequent measurements. Further, the TCPC group required higher CMV PIP for all measurements with statistically significant differences at admission, 6,12, and 24-hours post-procedure. Notably, for infants who underwent TCPC, RSS was similar to pre-procedural values within 6-hours of procedure; whereas, RSS increased in the SL group from 12 to 24-hours

(Appendix J). A larger proportion of the SL group received HFV ventilation at 24-hours compared with subjects who underwent TCPC (43% vs. 5%, $p = .004$). Temporal trends in mechanical ventilation and physiologic variables over all time periods are displayed in (Appendix K).

Table 6.

Respiratory Severity Score, Mechanical Ventilation and Physiologic Outcomes

Variable	SL (n = 88)	TCPC (n = 22)	<i>P</i>
RSS > 50%			
Post-procedure	23 (26%)	7 (32%)	.59
6-hours	22 (25%)	4 (18%)	.50
12-hours	35 (40%)	3 (14%)	.021*
24-hours	28 (32%)	3 (14%)	.09
PIP > 20%	5 (6%)	4 (18%)	.08
\bar{P}_{aw} >20%	27 (31%)	6 (27%)	.75
FiO ₂ >20%	68 (77%)	15 (68%)	.37
Hypotension	16 (18%)	1 (5%)	.19
PCLS	8 (9%)	1 (5%)	.68

Results are presented as *n* %. *RSS* = Respiratory Severity Score, *SL* = Surgical ligation, *TCPC* = Transcatheter PDA Closure, *PIP* = peak inspiratory pressure, \bar{P}_{aw} = mean airway pressure, *FiO₂* = Fraction of Inspired Oxygen, *PCLS* = Post cardiac ligation syndrome. * p -value < .05.

Outcomes at Disposition

Survival to discharge was 97% to 100% for SL and TCPC, respectively. Life support was withdrawn in three subjects in the SL group as a result of surgical NEC and sepsis; all of which occurred >25 days post-procedure. No statistical differences were observed between groups for reported medical or surgical NEC, ROP \geq stage 2, PMA at discharge, and weight at discharge. More infants in the TCPC group met the criteria for BPD \geq grade 3, however, this did not achieve statistical significance. Subjects in the TCPC group had a shorter ICU length of stay (4 days vs. 7 days, $p = .017$) and were larger at discharge (1115 g vs. 1440 g, $p = .033$). Twenty

subjects (91%) in the TCPC group were mechanically ventilated and 2 (9%) were supported with CPAP at the time of retro-transfer. For the SL group, 61 (72%) remained mechanically ventilated, 10 (12%) were supported with CPAP, 6 (7%) low-flow nasal cannula, and 8 (9%) were in room air at the time of transfer. Outcomes at disposition are displayed in Table 8.

Table 8.

Outcomes and Morbidity at Disposition

Outcome	SL (n = 88)	TCPC (n = 22)	<i>P</i>
Survived to DC	85 (97%)	22 (100%)	.99
ICU Length of Stay	7 (4-41)	4 (2-15)	.017*
NEC, medical	11 (13%)	2 (9%)	.99
NEC, surgical	17 (19%)	1 (4.5%)	.12
ROP \geq stage 2	9 (10%)	5 (23%)	.12
BPD \geq grade 3	7 (8%)	5 (23%)	.047
PMA at discharge, weeks	30.7 (28.7-34.2)	31.4 (28.8-35.7)	.22
Weight at discharge, g	1115 (865-1685)	1440 (1027-2325)	.033*

Note. DC = discharged from hospital or retro-transfer to referring center, ICU = intensive care unit, NEC = necrotizing enterocolitis, ROP = retinopathy of prematurity, BPD = bronchopulmonary dysplasia, and PMA = postmenstrual age. * $p < .05$.

Analysis 2: Comparison of subjects who required post-procedural HFV

Eighteen subjects were managed with HFV at admission, of which 8 continued to receive HFV post-procedure; 6 SL and 2 TCPC. Forty-eight subjects underwent HFV within 24-hours post-procedure and 62 were managed with conventional mechanical ventilation. Subjects who required HFV post-procedure were younger, more likely to be male, underwent definitive PDA closure earlier, and had smaller ductal diameter on echocardiogram (*Table 9*). Subjects who underwent post-procedural HFV demonstrated escalation of median RSS from pre-procedure through 24-hours, higher \bar{P}_{aw} and FiO_2 at 6, 12, and 24-hours post-procedure compared with the CMV cohort. Median pH was lower in the HFV group for all measurements and statistically significant from 6-hours through 24-hours post-procedure (Appendix L). Subjects managed with

HFJV (n= 38) had higher PEEP levels compared with the CMV group at 6, 12, and 24-hours post-procedure. HFJV on-time was maintained at 0.02 seconds with frequency at 7 Hz in all except two subjects; who were managed on 6 Hz with HFJV on-time 0.024 seconds. Median HFJV PIP and *IQR* was 22 (20-25.5), 22 (20-26), 26 (23-29) and 27.5 (23-30) for post-procedure, 6-hours, 12-hours and 24-hours, respectively. Ten subjects were managed on HFOV, median amplitude (ΔP) and *IQR* was 27 (24-30), 26 (24-30), 28 (24-32), and 27 (22-55) for post-procedure, 6-hours, 12-hours, and 24-hours, respectively.

Table 9.

Demographics: High-Frequency Ventilation vs. Conventional Mechanical Ventilation

Variable	HFV (n = 48)	CMV (n = 62)	<i>P</i>
Procedure type			
TCPC	4 (8.3%)	18 (29%)	.008*
Surgical ligation	44 (91.7%)	44 (71%)	
Gestational Age, weeks	25 (24, 26)	26 (24, 27)	.01*
Weight, kg	0.72 (0.59, 0.82)	0.77 (0.65, 0.9)	.073
Duration of MV, pre-admission	12 (7, 23)	19 (8, 27)	.075
PDA closure, day of life	19 (14, 26)	25 (18, 41)	.003**
PDA diameter, mm	2.5 (2, 3)	3 (2.5, 3.5)	.014*
Sex			
Female	16 (33.3%)	34 (54.8%)	.034*
Male	32 (66.7%)	28 (45.2%)	
PMA at admission, weeks	27 (25, 29)	29 (27, 32)	.001**

Note. Data are presented as n (%) or *Mdn* and *IQR*. *HFV* = high-frequency ventilation, *CMV* = conventional mechanical ventilation, *TCPC* = transcutaneous percutaneous device closure, *PDA* = patent ductus arteriosus, *PMA* = post-menstrual age. **p* < .05. ***p* < .01.

Discussion, Recommendations, and Conclusion

Discussion

The present study aimed to assess differences in post-procedural respiratory decompensation in a cohort of mechanically ventilated subjects who underwent SL or TCPC. The primary finding from our study is that 40% of infants who underwent SL demonstrated RSS (> 50%) above pre-procedural values at 12-hours post-procedure compared to 14% of the TCPC group, ($p < .021$). Moreover, 43% of the SL group was transitioned to HFV by 12-hours post-procedure and remain on HFV through 24-hours. Both groups were similar for sex, birthweight and gestational age, and other perinatal factors. The TCPC group was associated with older age at the procedure, longer duration of mechanical ventilation before PDA closure, larger PDA diameter, and LV dilation. Postmenstrual age was similar between groups at the time of transfer back to the referring center, however, TCPC was associated with a shorter length of stay on our unit.

Several investigations have found improvements in pulmonary status including a more rapid return to baseline RSS and shorter duration of mechanical ventilation in infants who underwent TCPC as compared to SL (Hazeem et al., 2013; Rodriguez-Ogando et al., 2018; Sathanandam et al., 2018; Balduf, et al., 2019). While we did not precisely measure the time of return to baseline RSS, infants in the TCPC group with clinically significant respiratory decompensation (exceeding RSS >50%) peaked at post-procedure and declined thereafter; in contrast, RSS >50% progressively increased in the SL cohort from 6 to 12-hours. These findings suggest that subjects who underwent TCPC exhibited a precipitous return toward baseline RSS within 6-hours of procedure in comparison to their surgical counterparts that demonstrated progressively higher levels of respiratory support from 6 to 12-hours post-procedure.

Although, the avoidance of thoracotomy and instrumentation of the lung to access the DA for ligation may be partially responsible for the observed differences in respiratory decompensation between groups; it is also plausible that larger PDA diameter (3.3 mm vs. 2.5 mm, $p = .002$) and a higher proportion of LV dilation (91% vs. 67%, $p = .033$) in the TCPC group may have contributed to improvements in post-procedural RSS. Krishnappa and colleagues (2019) reported on echocardiographic indices of PDA size and LV dilation as predictors of early extubation in a cohort of surgical ligated preterm infants dependent on mechanical ventilation. After adjustment for confounders, multivariable analysis demonstrated that PDA size > 2.5 mm aHR 0.51, 95% CI [0.36, 0.72] and LV dilation z score ≥ 2 aHR 0.61, 95% CI [0.42, 0.87] were independent predictors of early weaning and extubation. Therefore, it's conceivable that infants with larger PDA diameter and LV dilation may be more likely to have greater improvement in pulmonary compliance following ductal closure which facilitates weaning mechanical ventilation.

Unlike previous studies comparing SL to TCPC, we excluded all subjects who did not require invasive mechanical ventilation upon admission to assess differences between subjects who continued to receive conventional mechanical ventilation from those who underwent post-procedural HFV. There is a paucity of studies describing temporal escalation of RSS in context with the timing, level, or type of mechanical ventilation support in premature infants undergoing definitive PDA closure. Our findings are supported by Santhanandam et al. (2018), who reported a lower RSS delta change (18% vs. 76%, $p < .01$) for TCPC and SL, respectively. Additionally, these authors found that RSS was higher at baseline (3.9 vs. 2.8, $p = .18$) for TCPC and SL respectively. Importantly, post-procedural escalation of RSS was more pronounced in infants who underwent TCPC ≥ 8 weeks postnatal age, compared with those who received TCPC

≤ 4 weeks (5.4 vs. 3.4, $p = .01$). In the present study, median postnatal age at procedure was 29.5 days (>4 weeks) and may partially explain why the TCPC group required higher respiratory support (PIP, PEEP, \bar{P}_{aw}) than the less mature SL group. Infants in the TCPC group had longer exposure to HsPDA and underwent mechanical ventilation for twice as long; both of which have been associated with the development of BPD, however, causality has yet to be irrevocably determined (Clyman & Hills, 2020; Mirza et al., 2019; Schena et al., 2015). Collectively, these findings suggest that if TCPC is performed at an earlier age (e.g. < 4 weeks) it may be possible to mitigate prolonged exposure to and escalation of mechanical ventilation parameters. However, size limitations (Piccolo device is FDA approved for preterm infants >700 g), ductal morphology and infection status may prevent some infants from being candidates for TCPC (Backes et al., 2016; Backes et al., 2019).

The secondary analysis compared subjects who remained on conventional ventilation to those who underwent HFV within 24-hours of PDA procedure. Our findings suggest that HFV after PDA closure is associated with SL, smaller gestational age, male sex, younger age at PDA closure, smaller duct diameter, lower PMA at admission, and higher RSS from admission through 24-hours. Gestational age < 26 weeks, birthweight < 1 kg, PDA size, PDA procedure at < 28 postnatal days contribute to post-procedural cardiorespiratory instability and are established risk factors for the development of cardiopulmonary decompensation, chronic lung disease or death (El-Khuffash et al., 2013; Jain et al., 2012; P. J. McNamara et al., 2010; Natarajan et al., 2010; Teixeira et al., 2008). Consistent with these findings, subjects who required escalation to HFV post-procedure were younger, underwent PDA closure earlier, and were more likely to have undergone SL. Moreover, our finding that male sex was associated with HFV is consistent

with previous reports which suggested that female infants on average have lower respiratory morbidity and mortality compared to their male counterparts (Townsel et al., 2017).

Several authors have described derangement of oxygenation or ventilation status and escalation of RSS following PDA ligation (Francis et al., 2011; Hsu et al., 2019; Seo et al., 2020; Ting et al., 2016). Our findings are corroborated by Seo et al. (2020), who compared the respiratory parameters in a cohort of preterm infants who underwent PDA ligation (*Mdn* 22 days postnatal age) based on the binary outcome of prolonged ventilation >14 days vs. successful extubation in < 14 days. These authors found that less mature infants with lower birthweights were more likely to receive HFOV before (62% vs. 13%, $p = .004$) and after (67 % vs. 7 %, $p < .001$) PDA closure. Francis and colleagues (2013) evaluated temporal trends in respiratory and cardiovascular morbidity within 48-hours of SL and reported median baseline RSS 4.6 (3-6.1) and post-operative RSS 6 (3.5-8). Similar to the present study, RSS >50% was reported in 48% of infants following ligation and peaked at 42% by 12-hours. Currently, Serrano et al. (2019) is the only report which described post-procedural HFV requirement between SL and TCPC. These investigators found that 20% of infants who underwent SL received HFOV and observed no HFV requirement in the TCPC group. Further, the SL group demonstrated a higher post-procedural FiO_2 (0.64 vs. 0.43, $p = .004$) and a larger total change in peak FiO_2 (0.23-0.9, $p = .008$). These results underscore our findings that infants who underwent SL are more likely to present with respiratory decompensation within 12-hours of ligation and require rescue HFV more frequently than infants who underwent TCPC.

Strengths of the present study include a moderate sample size of mechanically ventilated preterm infants who underwent SL or TCPC at a large quaternary care center. To the best of our

knowledge, the current study is the first to compare temporal escalations of conventional mechanical ventilation and timing of transition to HFV between SL and TCPC.

There are several potential limitations to the present investigation. First, this is a retrospective, study in a single-center over an approximately 6-year period. The retrospective design is uncontrolled and uses existing data from the electronic medical record which were initially captured for purposes other than research. Therefore, one of the largest threats to internal validity is data that is missing or inaccurately documented. With this in mind, we purposely selected RSS to limit missing data, as mean airway pressure and FiO₂ are frequently recorded in the medical record. Second, SL for premature infants was the standard of care for HsPDA in infants who were unresponsive or not candidates for pharmacological treatment, until the Piccolo device received FDA approval in 2019 (Backes et al., 2019). Therefore, the ratio of infants who received ligation vs. TCPC was uneven (4:1) given the temporal changes in PDA management. Finally, we recognize that there may be other meaningful time points to consider beyond 24-hours of age. However, infants demonstrating stability following SL or TCPC are generally retro-transferred to the referring hospital within 48-hours of PDA procedure; whereas those who require HFV or escalated ventilator settings will have a longer LOS at Boston Children's Hospital. As such, we have reviewed short-term outcomes to better understand the escalation and phase of mechanical ventilator titration.

Recommendations

The management of preterm infants with PDA, such as timing and method of closure continues to be a contentious topic and is unlikely to be settled in the absence of well-designed randomized control trials. Nevertheless, we aim to further describe the prevalence of respiratory decompensation in both SL and TCPC with the aim of identifying high-risk phenotypes for

future research. Current initiatives include logistic regression modeling to further define risk factors for HFV and the development of a clinical score to assist bedside providers in the decision to utilize rescue HFV. Future projects will include validation of the clinical score and prospective collaboration with referral hospitals to assess long-term outcomes.

Conclusion

In this study, we found that respiratory decompensation following closure of the PDA was associated with younger gestational age, younger age at PDA closure, surgical ligation, and elevated RSS values over the first 12 hours after closure. These results confirm prior data, but also suggest that an elevated RSS following PDA closure may be a useful non-invasive bedside tool to identify the respiratory phenotype of post ligation cardiac syndrome.

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APPENDICES

Appendix A

Figure 1. Physiologic Manifestations of Prolonged Left-to-Right Shunt

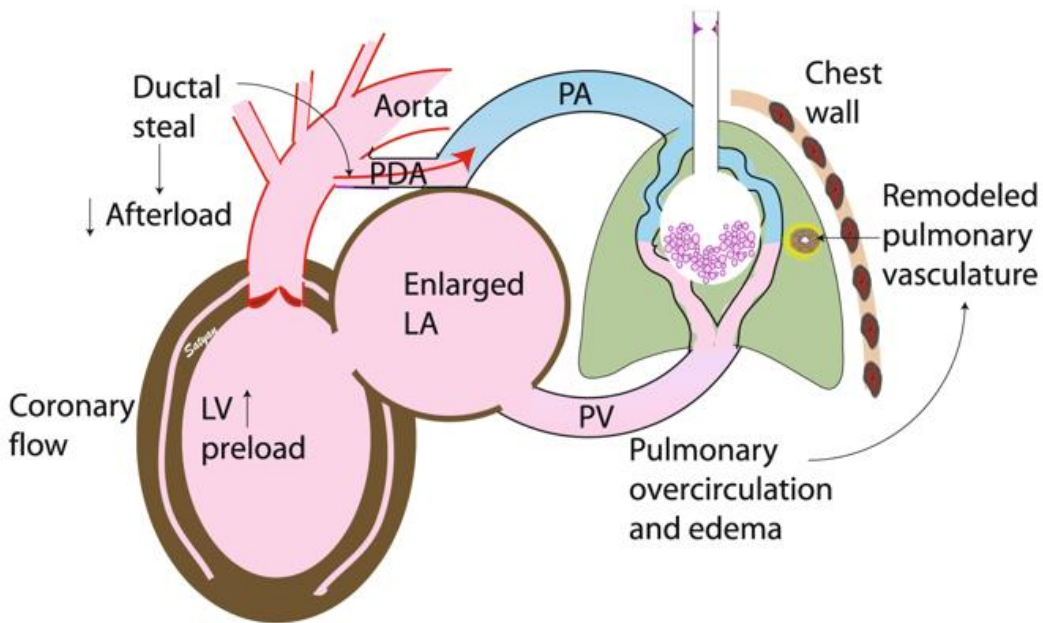


Figure 1. Schematic of the physiologic impact of prolonged exposure to left-to-right shunt from hemodynamically significant PDA. Pulmonary blood flow is increased as a result of blood being diverted from the systemic to pulmonary circulation. Importantly, the presence of a large shunt reduces left-ventricle afterload and the increases LV preload. The increase in blood flow to the pulmonary arteries and veins results in left atrial and ventricular dilation. Moreover, prolonged exposure to elevated pulmonary artery pressures can be the catalyst for pulmonary vascular remodeling and increased pulmonary vascular resistance. *PDA* = patent ductus arteriosus, *PA* = pulmonary artery, *PV* = pulmonary vein, *LA* = left atrium, *LV* = left ventricle. Reprinted with permission from “Patent Ductus Arteriosus in preterm infants: is early transcatheter closure a paradigm shift?” by P. Vali, S. Lakshminrusimha, A. Pelech & F.Ing, 2019, *Journal of Perinatology*, 38, p. 1454. Copyright 2019 by Satyan Lakshminrusimha.

Appendix B

Figure 2. A Comparison of Fetal and Postnatal Circulation

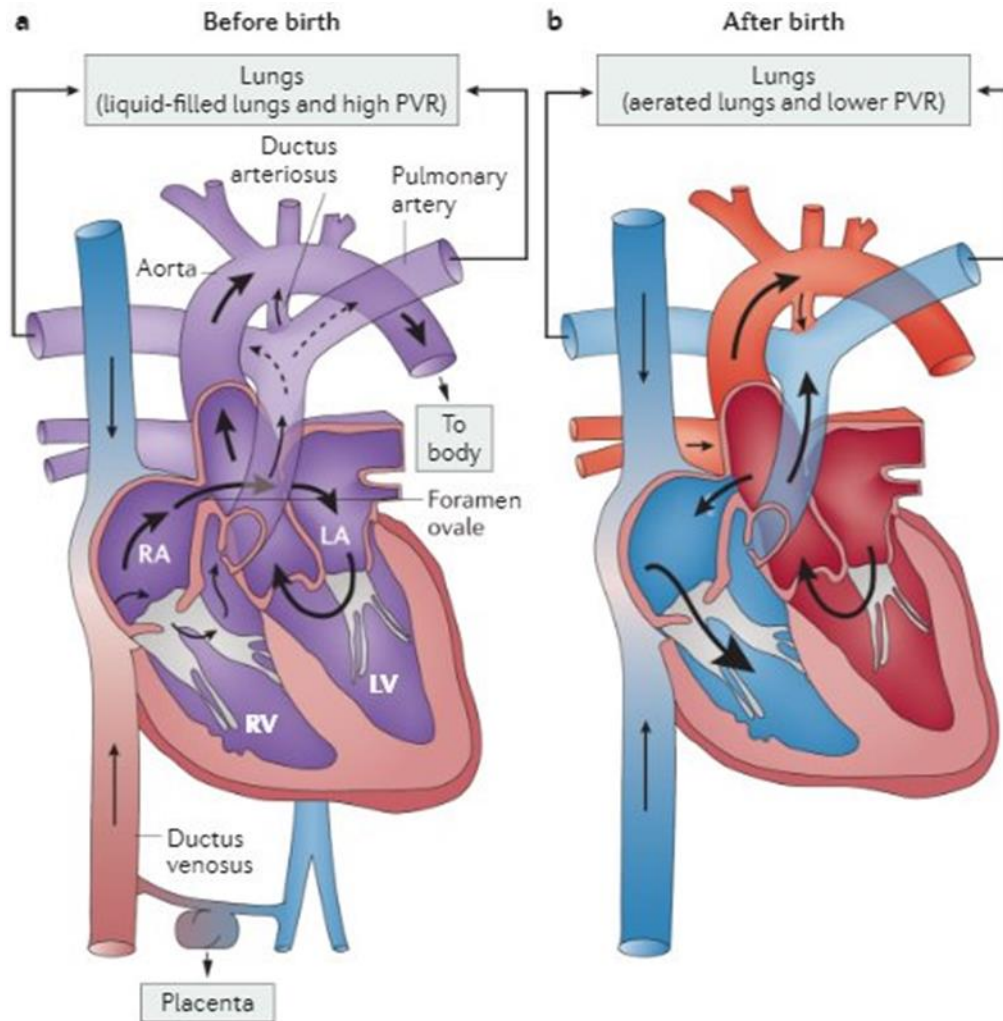
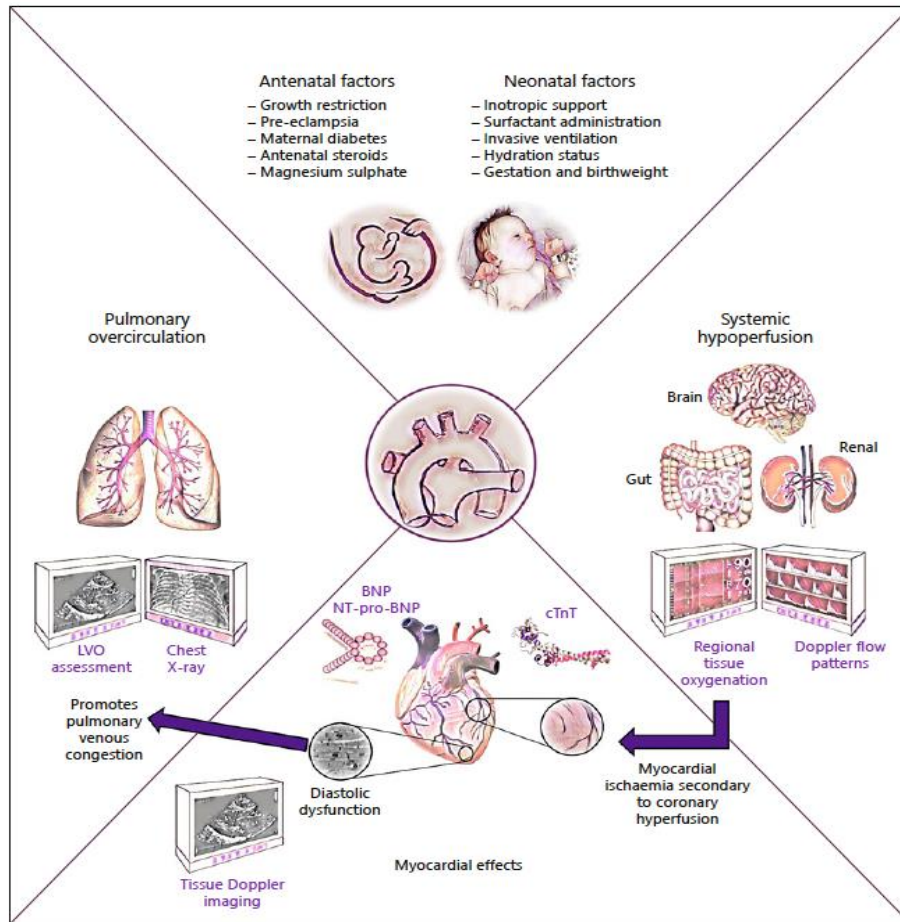


Figure 2. Schematic diagram of intrauterine and extrauterine circulation (a) fetal circulation is depicted (b) denotes neonatal circulation after birth. RA = right atrium, LA = left atrium, RV = right ventricle, LV = left ventricle, PVR = pulmonary vascular resistance. Reprinted with permission from “Patent Foramen Ovale,” by Homma et al., 2016, *Nature reviews*, 2, p. 1. Copyright 2016 by Macmillan Publishers Limited

Appendix C

Figure 3. Factors Which Contribute to Hemodynamic Significant PDA



Note. A comprehensive multi-modal evaluation using several different technologies and biomarkers allow for a more thorough estimation of PDA impact on organ function. *LVO* = left ventricular output, *BNP* = B-type natriuretic peptide, *NT-pro-BNP* = N-terminal pro-B-type natriuretic peptide, *cTnT* = cardiac troponin T. Reprinted with permission from “Defining ‘Haemodynamic Significance’ of the Patent Ductus Arteriosus: Do We Have All the Answers,” by A. Smith, and A.F EL-Khuffash, 2020, *Neonatology*, p. 4. Copyright 2020 by Karger AG.

Appendix D

Figure 4. Schematic of the Relationships Governing Blood Flow Through a Vessel

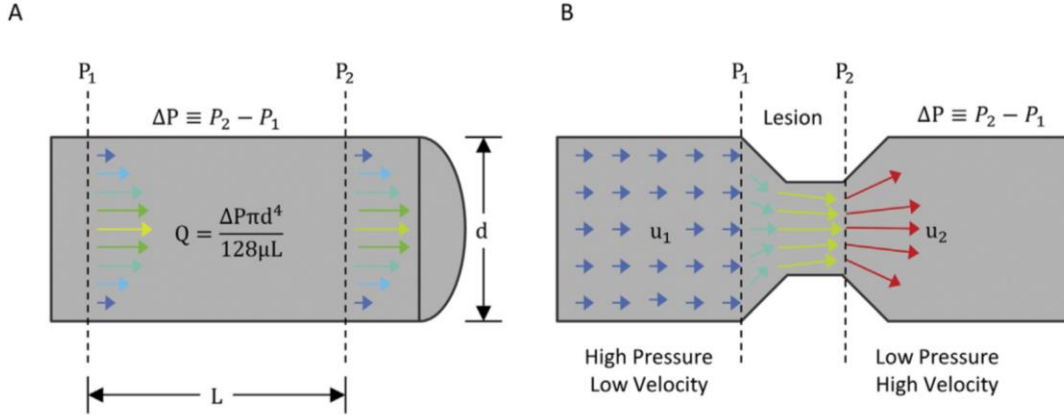


Figure 4. (A) Poiseuille's equation describes the relationship between flow and pressure during laminar flow. Q = flow, ΔP = pressure gradient $P_2 - P_1$; $\pi = 3.14$, d = diameter⁴, μ = dynamic viscosity, and L = vessel length. At a constant pressure gradient, the magnitude of blood flow through a vessel is determined by the resistance. Resistance is most influenced by small changes in vessel diameter. (B) Bernoulli's Principle states that blood flow velocity and pressure drop through a lesion (e.g. PDA) is related to flow rate and cross-sectional area of the vessel. u^1 = low velocity, u^2 = high velocity. Reprinted with permission from "Mechanical Concepts Applied in Congenital Heart Disease and Cardiac Surgery," by R. B. Gerrah, S. J. Haller, and I. George, 2017, *Annals of Thoracic Surgery*, 103, p. 2007. Copyright 2017 by The Society of Thoracic Surgeons.

Appendix E

Figure 5. Physiologic Manifestations of Post Cardiac Ligation Syndrome

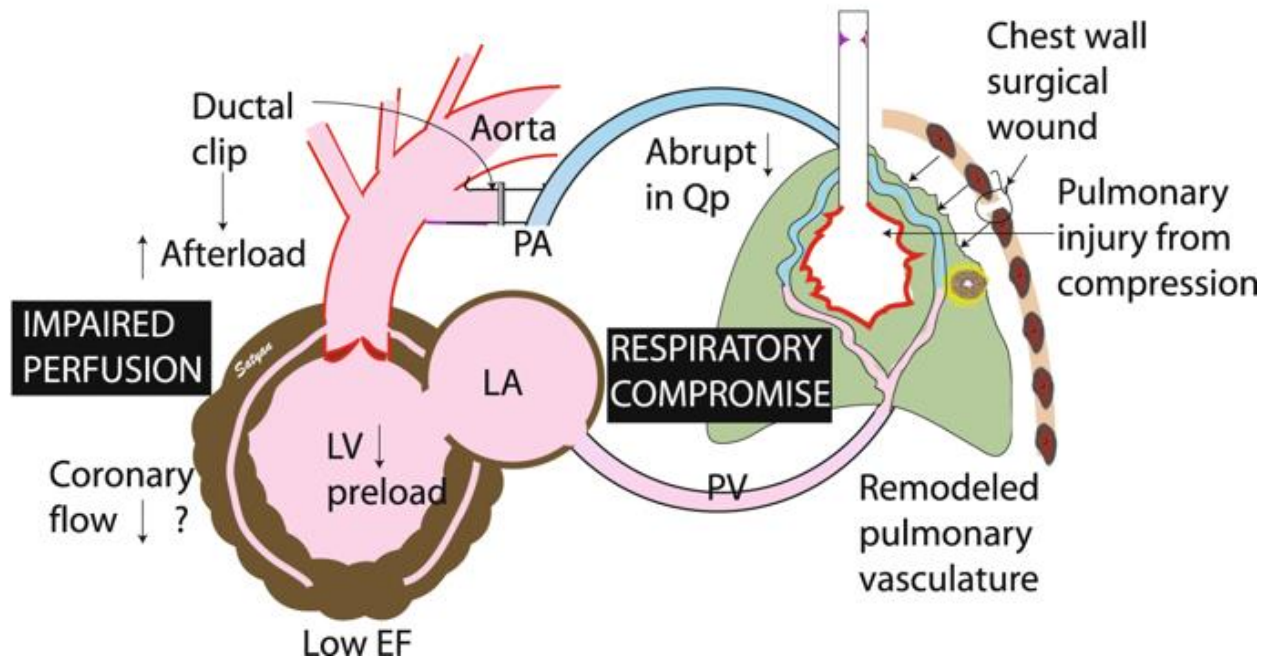


Figure 5. Schematic of the physiologic manifestations of post cardiac ligation syndrome. Ligation of the PDA results in an immediate decrease in pulmonary blood flow, increased LV afterload and concurrent reduction of LV preload. The premature myocardium is unable to handle this abrupt change in loading conditions and may be further limited by coronary hypoperfusion, ventricular dysfunction and systemic hypoperfusion. *PDA* = patent ductus arteriosus, *PA* = pulmonary artery, *Qp* = pulmonary blood flow, *PV* = pulmonary vein, *LA* = left atrium, *LV* = left ventricle, *EF* = ejection fraction. Reprinted with permission from “Patent Ductus Arteriosus in preterm infants: is early transcatheter closure a paradigm shift?,” by P. Vali, S. Lakshminrusimha, A. Pelech & F. Ing, 2019, *Journal of Perinatology*, 38, p. 1454. Copyright 2019 by Satyan Lakshminrusimha.

Appendix F

Figure 6. Transcatheter PDA Closure

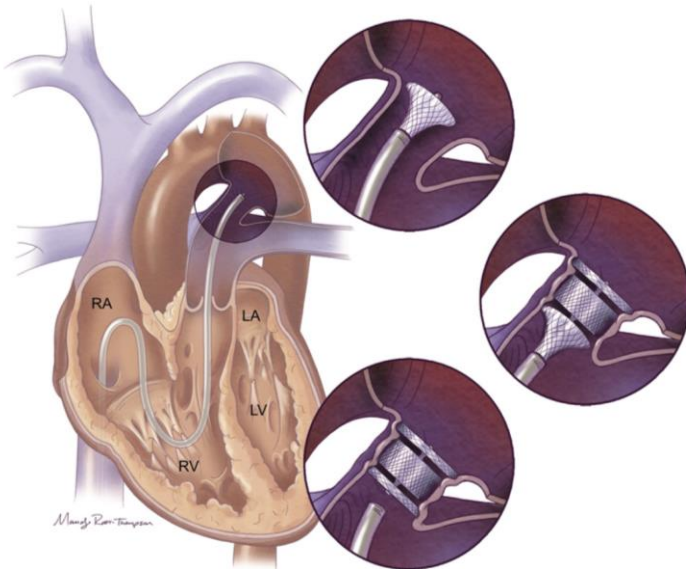


Figure 6. Schematic denoting the transvenous approach for transcatheter closure of the PDA. Access is obtained via the femoral vein and the catheter is advanced up the inferior vena cava to the right atrium, across the tricuspid valve, the right-ventricle, across the pulmonary valve, pulmonary artery and finally into the PDA. The device is subsequently deployed in the PDA under echocardiography and fluoroscopic guidance. RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle, EF = ejection fraction. Reprinted with permission from “Percutaneous Closure of the Patent Ductus Arteriosus in Very Low Weight Infants: Considerations Following US Food and Drug Administration Approval of Novel Device” by C. H. Backes et al., 2019, *Journal of Pediatrics*, 213, p. 219. Copyright 2019 by Elsevier.

Appendix G

Table 3.

Comparison of Respiratory Outcomes Between Surgical Ligation and TCPC

First author	N	Age, weeks	Weight, kg	Design	Primary Outcome Measured
Hazeem	16				
SL	8	29 (23-37)	2.8 (2.3-4.2)	Single-center, retrospective case-control, matched-pairs, comparison of mechanically ventilated infants < 4kg	Median time of return to baseline RSS SL: 53 hours (13-219) vs. TCPC: 17 hours (0-113), $p < .05$. Baseline RSS was 2.6 (1.4-6) and 4.4 (1.3-14.6) for SL and TCPC respectively
TCPC	8	29.8 (24-39)	1.55 (0.52-2.97)		
Ogando	78				
SL	53	25.8 \pm 2	0.79 \pm 0.25	Single-center, retrospective comparison of infants requiring mechanical ventilation	Pulmonary score decreased in both groups (linear mixed effect model, $p < .001$ TCPC group had a more rapid recovery, beginning immediately after ductal closure vs. 7 days in SL group
TCPC	25	26.5 \pm 1.2	0.92 \pm 0.22		
Regan	147				
SL	83	25.3 (24.7-26.9)	0.76 (0.69-0.98)	Multicenter, retrospective, matched-pairs (2:1), case-control study of respiratory outcomes in infants < 3kg	Duration of mechanical ventilation was shorter in TCPC group 3 (0-7) compared with SL 5 (2-14) days, $p = .035$. This effect was more pronounced if ductal closure was completed prior to 4 weeks (3 vs. 9 days, $p = .022$)
TCPC	64	25.6 (24.7-27.0)	0.78 (0.70-0.95)		
Sathanandam	120				
SL	40	25 (23-27)	0.69 (0.56-0.97)	Retrospective, propensity-score matched (2:1) study of infants to evaluate changes in RSS (before/after intervention)	Greater increase in RSS following SL compared with TCPC (76% vs. 18%, $p < 0.01$). Longer time to return to baseline RSS following SL compared with TCPC (28 vs. 8.4 hours, $p < .01$)
TCPC	80	25 (23-27)	0.70 (0.57-0.83)		
Serrano	84				
SL	59	25.9 \pm 1.8	0.79 \pm 0.28	Retrospective, cohort study of VLBW infants to evaluate escalation of respiratory support and PCLS	SL higher need for hemodynamic support than TCPC (20 % vs. 0, $p = .016$); higher post-procedure FiO_2 (0.64 vs. 0.43, $p = .004$; and absolute change in FiO_2 (0.23 vs. 0.09, $p = .008$). 20% of SL required HFOV
TCPC	25	25.2 \pm 1.79	0.76 \pm 0.18		

Data are presented as median, interquartile range or mean \pm standard deviation. *SL* = surgical ligation, *TCPC* = transcatheter PDA closure, *RSS* = respiratory severity score, *FiO₂* = fraction of inspired oxygen, *HFOV* = high-frequency oscillatory ventilation, *VLBW* = very low birthweight infant (< 1500 grams) and *PCLS* = post cardiac ligation syndrome

Appendix H

Figure 7. Flow Diagram of Included and Excluded Subjects

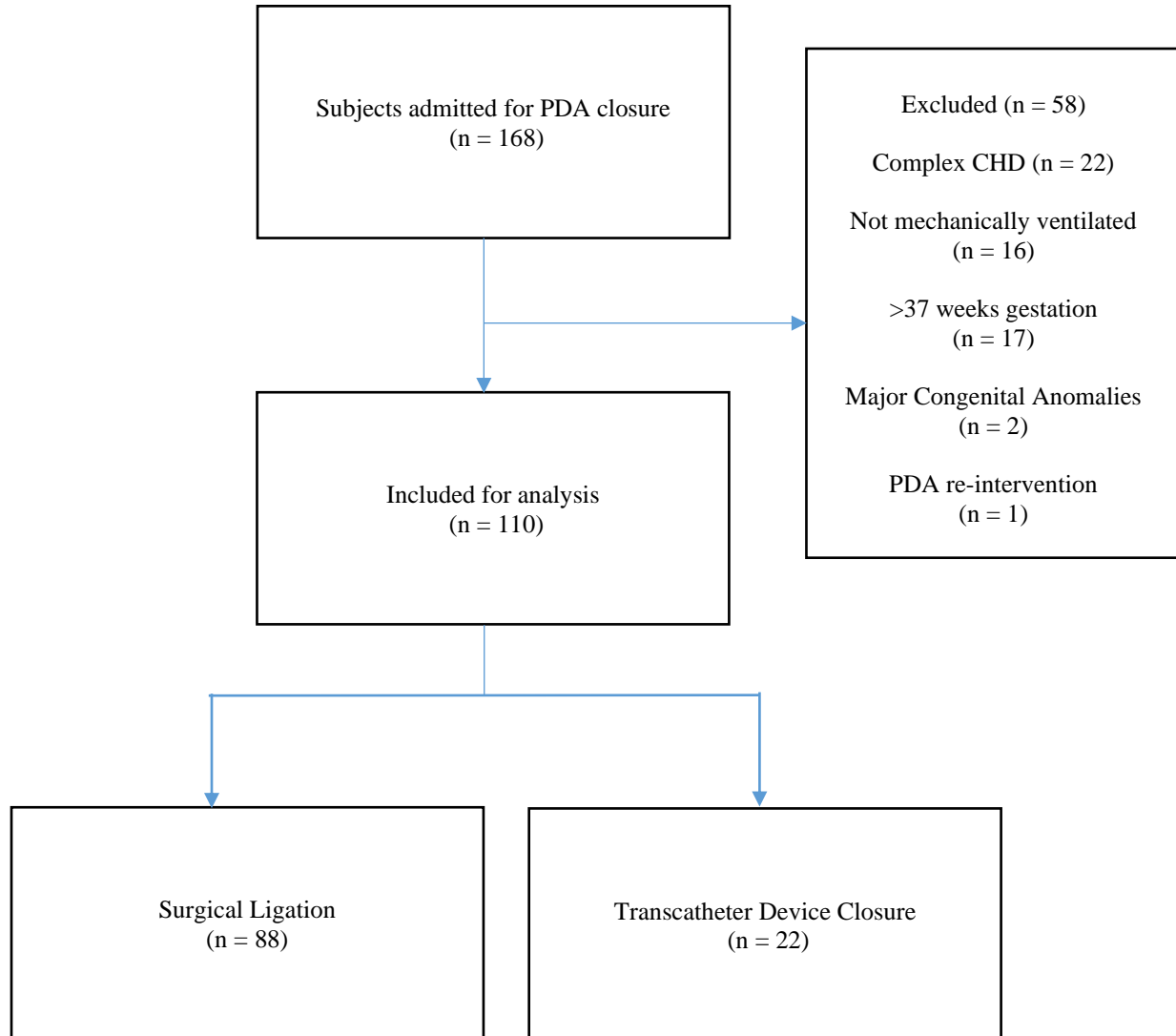


Figure 7. CHD = Congenital Heart Disease

Appendix I

Table 4.
Demographics and Perinatal Factors Between Groups

Variable	SL (n = 88)	TCPC (n = 22)	P value
Sex			
Male	52 (59%)	14 (64%)	.81
Female	36 (41%)	8 (36%)	
Gestational Age, weeks	25.1 (24.1-26.3)	25.6 (24.9-27.0)	.17
PMA, weeks	27.9 (26.1-29.4)	30.1 (28.5-35.2)	.001**
Extremely premature	81 (92%)	20 (91%)	.65
Very premature	7 (8%)	2 (9%)	.99
Birthweight, g	750 (640-895)	663 (581-810)	.12
ELBW, < 1000g	81 (92%)	17 (77%)	.061
VLBW, < 1500g	5 (6%)	4 (18%)	.08
LBW, < 2500g	2 (2%)	1 (5%)	.49
Apgar, 1 minute	3 (1-6)	3.5 (2-6)	.36
Apgar, 5 minutes	7 (4-8)	6.5 (5-8)	.59
Surfactant	81 (92%)	20 (91%)	.99
Cesarean	63 (72%)	15 (68%)	.79
IUGR	6 (7%)	1 (5%)	.99
Antenatal Steroids	18 (46%)	7 (50%)	.27
Postnatal Steroids	30 (34%)	10 (47%)	.33
IVH \geq Grade 3	21 (24%)	2 (9%)	.15
Medical NEC	11 (13%)	2 (9%)	.99
Surgical NEC	17 (19%)	1 (5%)	.17
Ventilator duration, days	13 (6.2-23.8)	26 (21-48)	.001**
Ventilator mode			.74
CMV	75 (85%)	18 (82%)	
HFV	13 (15%)	4 (18%)	
PDA diameter, mm	2.5 (2.2-3.0)	3.3 (2.9-3.7)	.002**
PDA procedure, day ^a	20 (14-27)	29.5 (23-55)	.001**
Left-to-right shunt	84 (95%)	20 (90%)	.34
Dilated LA	66 (75%)	20 (95%)	.15
Dilated LV	59 (67%)	20 (91%)	.033**
Systolic gradient, mm Hg	20 (15-25)	25 (14.8-35)	.33
Flow reversal ^b	60 (68%)	17 (77%)	.45

Data are presented as median (interquartile range) for continuous variables and n % for categorical variables. *P* values were calculated using Fisher's exact test or the Mann-Whitney *U* test. *PMA* = Post menstrual age at NICU admission, *ELBW* = extremely low birthweight infant, *VLBW* = very low birthweight infant, *LBW* = low birthweight infant, *IUGR* = intrauterine growth restriction, *IVH* = intraventricular hemorrhage, *NEC* = necrotizing enterocolitis, *CMV* = conventional mechanical ventilation, *HFV* = high-frequency ventilation, *LA* = left atrium, *LV* = left ventricle. **p* < .05. ** *p* < .01.

^a Day of life PDA closure was performed.

^b Flow reversal = echocardiographic observation of flow reversal during diastole in the descending aorta

Appendix J

Figure 8.

Temporal Trends in Respiratory Severity Score

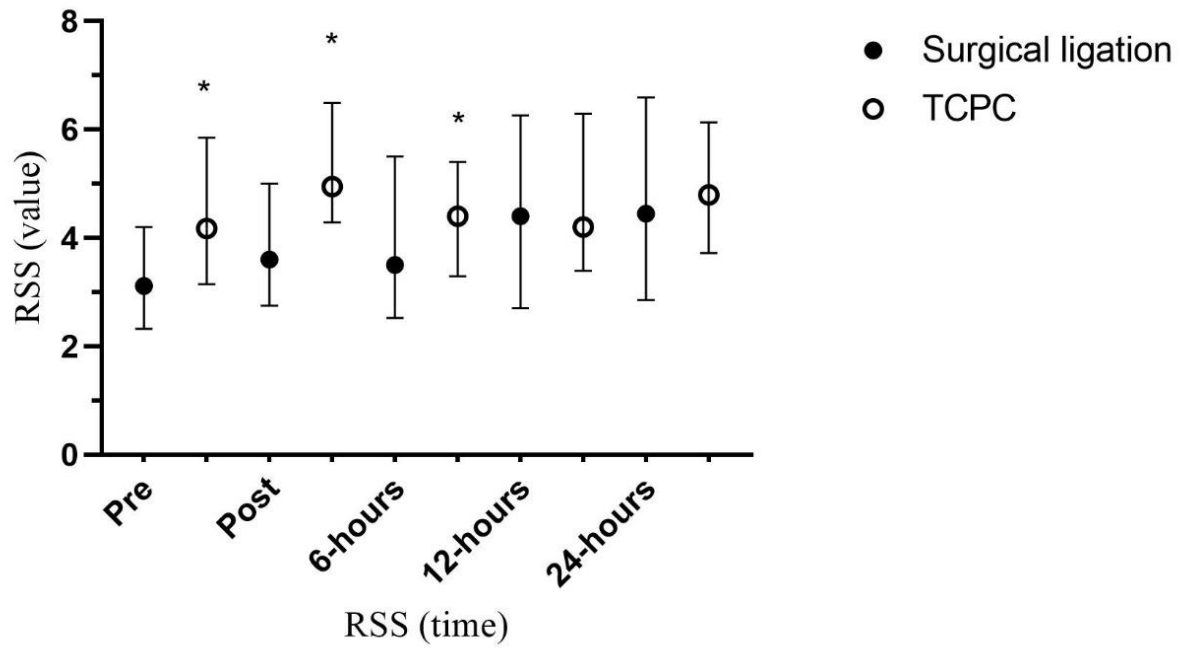


Figure 8. Data presented as *Mdn* and *IQR*. RSS = Respiratory Severity Score, TCPC = transcatheter PDA closure. * $p < .05$.

Appendix K

Table 7.
Mechanical Ventilation and Physiologic Characteristics: SL vs. TCPC

Variable	SL (n = 88)	TCPC (n = 22)	P
Pre-procedure			
RSS	3.8 (2.8-5.9)	5.4 (4.1-13)	.024*
CMV PIP, cm H ₂ O	21 (19-23)	23 (20-26)	.063
V _T , mL/kg	6 (5-8)	7 (6-8)	.50
f, breaths/min	35 (28-40)	32 (28-38)	.56
PEEP, cm H ₂ O	6(6-7)	7 (6-8)	.002**
FiO ₂	.3 (.25-.40)	.4 (.3-.46)	.020*
P _{aw} , cm H ₂ O	10 (9-11)	11.5 (10-14)	.001**
pH	7.27 (7.23-7.32)	7.31 (7.25-7.35)	.13
PCO ₂ , mm Hg	60.5 (53-67)	58 (46-71)	.94
HFV, n %	6 (18%)	2 (9%)	.97
Post-procedure			
RSS	3.1 (2.3-4.2)	4.2 (3.2-5.9)	.020*
CMV PIP, cm H ₂ O	21 (19-23)	23 (20-27)	.055
V _T , mL/kg	7 (6-8)	7 (6-9)	.68
f, breaths/min	36 (32-40)	34 (28-40)	.31
PEEP, cm H ₂ O	6 (6-6)	7 (6-7)	.003**
FiO ₂	.35 (.3-.5)	.47 (.40-.63)	.02*
P _{aw} , cm H ₂ O	10 (9-11)	11.5 (11-14)	.001**
pH	7.28 (7.17-7.37)	7.31 (7.23-7.39)	.31
PCO ₂ mm Hg	58 (46-71)	59 (45-69)	.94
HFV, n %	16 (18%)	3 (14%)	.97
6-hours			
RSS	3.6 (2.5-5)	4.4 (3.3-5.4)	.34
CMV PIP, cm H ₂ O	21 (19-22)	23 (22-32)	.006**
V _T , mL/kg	7 (6-8)	8 (6-10)	.09
f, breaths/min	38 (34-40)	36 (36-40)	.30
PEEP, cm H ₂ O	6 (6-6)	7 (6-7)	.003**
FiO ₂	.35 (.28-.49)	.40 (.30-.45)	.71
P _{aw} , cm H ₂ O	10 (9-11)	12 (11-13)	.006**
pH	7.27 (7.18-7.32)	7.32 (7.25-7.36)	.053
PCO ₂ , mm Hg	59 (50-68)	60 (50-64)	.94
HFV, n %	24 (27%)	3 (14%)	.27
12-hours			
RSS	4.4 (2.7-6.3)	4.2 (3.4-6.3)	.65
CMV PIP, cm H ₂ O	22 (19-23)	23 (22-27)	.011*
V _T , mL/kg	8 (7-10)	9 (7-9)	.68
f, breaths/min	36 (32-40)	33 (29-37)	.20
PEEP, cm H ₂ O	6 (5-6)	7 (6-7)	.003**
FiO ₂	.40 (.30-.53)	.41 (.30-.49)	.74
P _{aw} , cm H ₂ O	11 (10-12)	13 (10-14)	.005**
pH	7.27 (7.21-7.34)	7.34 (7.28-7.37)	.13
PCO ₂ , mm Hg	56 (49-67)	56 (50-63)	.94
HFV, n %	38 (43%)	4 (18%)	.048
24-hours			
RSS	4.5 (2.9-6.6)	4.8 (3.7-6.1)	.65
CMV PIP, cm H ₂ O	21 (18-23)	24 (22-28)	.004**
V _T , mL/kg	7 (6-8)	7 (7-9)	.68
f, breaths/min	34 (30-40)	32 (27-38)	.56
PEEP, cm H ₂ O	6 (6-6)	7 (6-8)	.003**
FiO ₂	.40 (.30-.53)	.40 (.35-.55)	.71
P _{aw} , cm H ₂ O	11 (9-13)	12 (10-13.5)	.14
pH	7.32 (7.24-7.36)	7.33 (7.31-7.37)	.13
PCO ₂ , mm Hg	55 (48-62)	53 (44-57)	.88
HFV, n %	38 (43%)	1 (5%)	.004**

Table 7. Results are presented as median (interquartile range). SL = surgical ligation, TCPC = transcatheter PDA closure, CMV PIP = conventional mechanical ventilation peak inspiratory pressure, V_T = exhaled tidal volume, PEEP = positive end-expiratory pressure, f = set respiratory rate, FiO₂ = Fraction of Inspired Oxygen, P_{aw} = mean airway pressure, SpO₂ = oxygen saturation, PCO₂ = partial pressure of carbon dioxide via blood gas, HFV = high-frequency ventilation. *p < .05. **p < .01.

Appendix L

Table 10.

Comparison of Post-procedural CMV with HFV

Variable	CMV (n = 62)	HFV (n = 48)	P
Post-procedure			
PEEP, cm H ₂ O	6 (6-7)	6 (6-8)	.27
\bar{P}_{aw} , cm H ₂ O	10 (9-11)	11 (10-12)	.07
FiO ₂	.36 (.30-.50)	.40 (.30-.57)	.06
RSS	3.7 (2.7-5)	4.2 (3.1-7.1)	.022*
pH	7.30 (7.24-7.38)	7.25 (7.13-7.38)	.34
PCO ₂ , mm Hg	59 (46-68)	58 (44-72)	.90
6-hours			
PEEP, cm H ₂ O	6 (6-7)	7 (6-8)	.008**
\bar{P}_{aw} , cm H ₂ O	10 (9-11)	11 (10-12)	.026*
FiO ₂	.32 (.25-.40)	.40 (.30-.55)	.002**
RSS	3.3 (2.5-4.5)	4.4 (2.9-6.3)	.001**
pH	7.31 (7.24-7.35)	7.22 (7.15-7.30)	.003**
PCO ₂ , mm Hg	56.4 (49.2-64)	64 (50-69)	.20
12-hours			
PEEP, cm H ₂ O	6 (6-7)	8 (6-9)	.004**
\bar{P}_{aw} , cm H ₂ O	10 (9-12)	12 (11-14)	.004**
FiO ₂	.35 (.25-.45)	.50 (.38-.64)	.004**
RSS	3.4 (2.5-5.2)	5.6 (4.2-8.9)	.004**
pH	7.31 (7.26-7.36)	7.25 (7.18-7.35)	.038*
PCO ₂ , mm Hg	56.9 (50.3-64.6)	55 (46-69.5)	.90
24-hours			
PEEP, cm H ₂ O	6 (6-7)	8 (7-10)	.004**
\bar{P}_{aw} , cm H ₂ O	10 (9-12)	12 (11-14)	.004**
FiO ₂	.35 (.25-.41)	.50 (.40-.60)	.004**
RSS	3.6 (2.7-5.2)	6.3 (4.5-8.2)	.004**
pH	7.34 (7.31-7.38)	7.28 (7.21-7.33)	.004**
PCO ₂ , mm Hg	50.2 (46.1-58.1)	57.5 (48-65)	.062

Table 10. Results are presented as median (interquartile range). CMV = conventional mechanical ventilation, HFV = high-frequency ventilation, PEEP = positive end-expiratory pressure for conventional ventilation (left) and high-frequency jet ventilation (right), \bar{P}_{aw} = mean airway pressure for conventional ventilation (left) and high-frequency jet ventilation or high-frequency oscillatory ventilation (right), FiO₂ = Fraction of Inspired Oxygen, RSS = Respiratory Severity Score, PCO₂ = partial pressure of carbon dioxide via blood gas. * $p < .05$. ** $p < .01$.